



Peripheral Vascular Diseases

Purpura

- Purpura is defined as visible hemorrhage into the skin or mucous membranes.
- Purpura may be primary (hemorrhage is an integral part of lesion formation) or secondary (secondary hemorrhage into established lesions e.g. stasis dermatitis).
- **Purpuric lesions are divided into six subsets:**
 1. Petechiae.
 2. Macular purpura.
 3. Macular ecchymoses.
 4. Palpable purpura.
 5. Non-inflammatory retiform purpura.
 6. Inflammatory retiform purpura.
- Two major causes of purpura: Microvascular occlusion syndromes and vasculitis.



Purpura^①

It is a blue-brown discoloration of skin or mucous membranes due to extravasation of RBCs from the vasculature into the skin. It **doesn't blanch** with diascopy, in contrast to erythema.

Purpuric lesions are divided into six subsets (Figs 1-6):

1. Petechiae (≤ 4 mm in diameter).
2. Macular purpura (5-9 mm).
3. Macular ecchymoses (≥ 1 cm).
4. Palpable purpura.
5. Non-inflammatory retiform purpura (the most typical presentation of microvascular occlusion syndromes).
6. Inflammatory retiform purpura (early lesions typically exhibit prominent erythema).

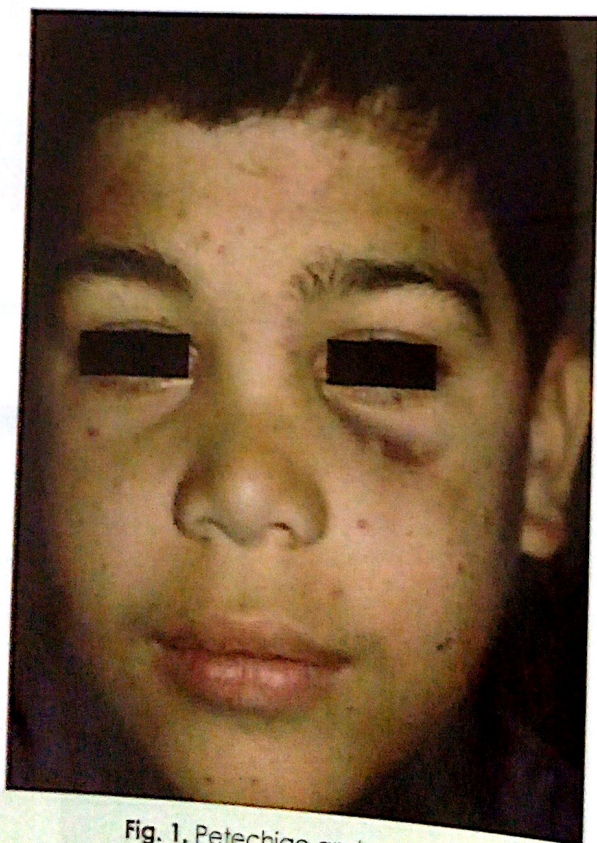


Fig. 1. Petechiae and purpura

Classification of purpura

Intravascular causes

- Decreased platelets (thrombocytopenia):
 - Defective production: Due to drugs, radiation, malignancy, uremia, infections, splenomegaly.
 - Increased destruction: Platelet auto-antibodies (ITP), thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, transfusion reactions, sequestration as in splenomegaly or extensive hemangiomas.
- Increased platelet count (thrombocytosis).
- Coagulation defects: Which may be congenital or acquired, e.g. lupus anticoagulant, anti-phospholipid antibody, coumarin necrosis.

Extravascular causes

- Purpura simplex, senilis, steroid therapy.
- CTDs, e.g. Ehlers-Danlos syndrome, pseudoxanthoma elasticum, amyloidosis, scurvy.
- Mechanical, e.g. external obstruction, trauma.
- Immunological defects: Autoerythrocyte sensitization syndrome.
- Toxins: Venoms.

Vascular causes, e.g. vasculitis.



Fig. 2. Petechiae and purpura

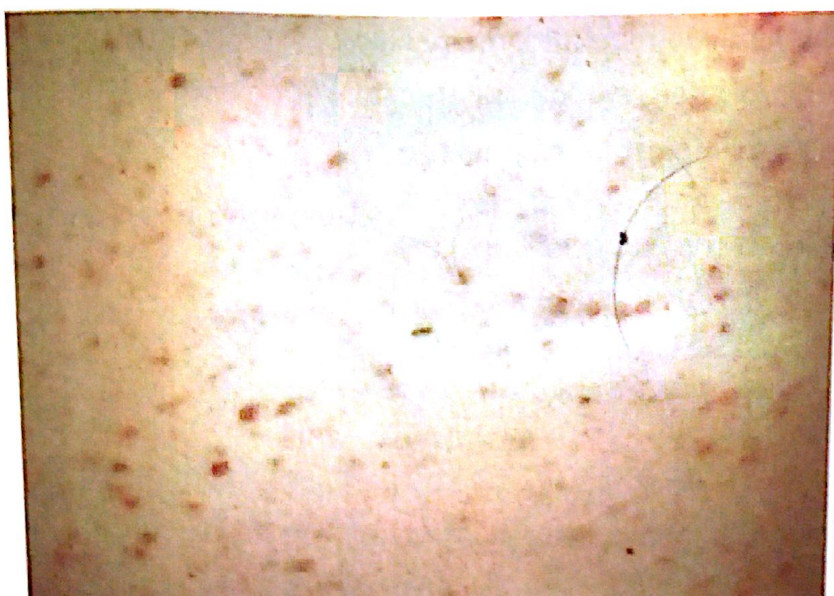


Fig. 3. Petechiae and purpura

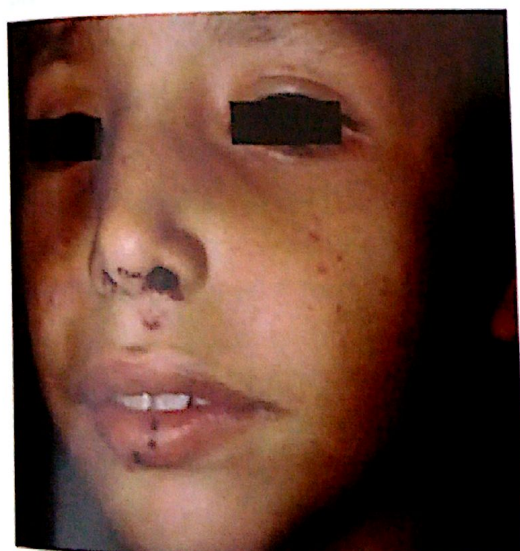


Fig. 4. Petechiae and purpura

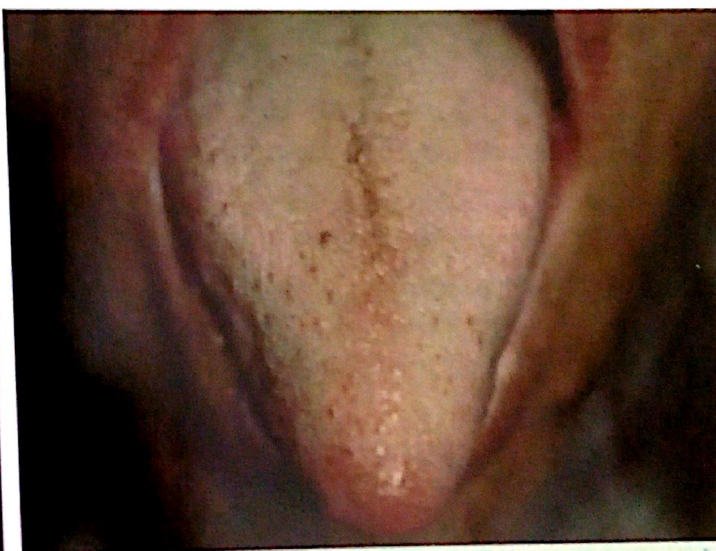


Fig. 5. Petechiae in the tongue



Fig. 6. Macular purpura and ecchymosis

Purpura: Mechanism & morphology

- **Simple hemorrhage** → Petechiae, ecchymoses (non-palpable, no erythema).
- **Inflammatory hemorrhage** →
 - Classical palpable purpura.
 - Inflammatory retiform purpura.
 - Target lesions.

- **Occlusion with hemorrhage** →
 - Non-inflammatory retiform hemorrhage.
 - Branching or stellate purpura.

Direct microscopic examination (capillary microscope) may be helpful in determining whether blood is intravascular or extravascular. It can be seen in nail fold capillary when not present elsewhere in the skin.

I) Intravascular causes

Thrombocytopenia $<50,000/\text{cmm}$, of normally functioning platelets, usually results in hemorrhage.

Idiopathic thrombocytopenic purpura "ITP"

- It is an autoimmune disorder characterized by petechiae & ecchymoses in the skin & mucous membranes and may be hemorrhages from nose, mouth or other internal organs.
- It most commonly affects children, in its acute form, where the onset may follow an upper respiratory tract viral infection.
- Thrombocytopenia usually lasts 2-4 weeks & then spontaneously resolves. Relapses are very rare.

Treatment

- Corticosteroids.
- Immunoglobulins.
- Danazol.
- Splenectomy.

Thrombotic thrombocytopenic purpura "TTP"

It is an acute condition with fulminant course characterized by 5 features:

1. Thrombocytopenic purpura leading to petechiae, ecchymoses and may be hemorrhages in the skin. Hematuria and hemoptysis may occur.
2. Microangiopathic hemolytic anemia, with jaundice.
3. Neurologic signs.
4. Renal manifestations.
5. Fever.

Cutaneous/systemic coagulopathies

Protein C or S abnormalities

- Neonatal purpura fulminans.
- Coumadin necrosis.
- Sepsis/DIC purpura fulminans.
- Post-infective purpura fulminans.
- Some antiphospholipid syndromes.

Antiphospholipid antibody syndrome.

The 1ry defect may be a vascular endothelial injury followed by adherence of platelets & fibrin. There is platelet consumption in the occluding platelet thrombi.

Treatment

- Corticosteroids in large doses with or without splenectomy.
- Plasma exchange therapy.

Purpura fulminans (Disseminated intravascular coagulation – DIC)

Purpura fulminans (PF) is a rare syndrome of progressive hemorrhagic necrosis of the skin, characterized by septicemia, shock and DIC. It occurs more commonly in children but has been reported in adults.

There are 3 types of PF:

1. **Protein C or S deficiency neonatal PF:** Congenital deficiencies of protein C and protein S are the most common cause of neonatal PF. Protein C is vitamin K-dependent serine protease which has natural anticoagulant & fibrinolytic activities. Activated protein C is enhanced in its anticoagulant activity by protein S, another Vit. K-dependent protein.

Causes of proteins C & S deficiency

- Congenital.
- Physiological in neonatal and childhood periods.
- Liver disease.
- Respiratory distress syndrome.
- DIC.
- Acute viral or bacterial infections.

Clinically: It usually appears 2-12 hours after birth with diffuse and symmetric purpura and sharply demarcated ecchymoses that evolves within hours into hemorrhagic bullae and purple-black areas of necrosis. They commonly affect buttocks, extremities, trunk and scalp.

Treatment:

- Fresh-frozen plasma or prothrombin complex concentrate (as a source of protein C or S) or protein C concentrate. Repeated infusions are necessary because of the short half-life (6-26 hours) of protein C.
 - Long-term treatment with oral anti-coagulants, starting at very low doses and under protective replacement therapy, to avoid coumarin-induced skin necrosis.
2. **Sepsis-associated PF:** It occurs during severe bacterial infections, e.g. *Neisseria meningitidis*, streptococci, *Hemophilus influenza* and others. Bacteria are usually absent from smears of the lesions. In this type of PF, endotoxin mediates the activation of the intrinsic pathway of coagulation and stimulates the release of cytokines with subsequent shock, consumption of proteins C & S and DIC.

Treatment: Management of the underlying infection and shock is a must.

3. **Idiopathic (classic) PF:** It occurs during the convalescent phase of benign infectious diseases most commonly involving the skin, as streptococcal infections, varicella or febrile exanthems. The patient appears severely-ill, with fever and prostration. There are indurated, painful purpuric lesions with sharp irregular geographic borders in a symmetric distribution affecting the buttocks and thighs. Full-thickness skin necrosis is usually seen.

Pathogenesis: During the preceding event, keratinocytes and endothelial cells produce IL-1 and TNF → pre-coagulant and antifibrinolytic changes in the dermal vascular endothelium → clotting and consumption of protein C & S and antithrombin III.

Histopathology: Occlusion of dermal capillaries and venules by thrombi with hemorrhage and varying degrees of cutaneous necrosis and mild perivascular inflammatory infiltrate.

Treatment:

- Supportive measures.
- Treatment of precipitating infections.
- Heparin IV.
- Fresh frozen plasma, hyperbaric O₂ and dextran.
- Surgery: Debridement, skin grafting or amputation.

Coumarin necrosis: Rarely, patients receiving oral anticoagulant, show, between the 3rd day and 10th days of therapy, single or multiple areas of ecchymosis that progress rapidly to central blistering and necrosis. The condition was found to be due to a deficiency of protein C, like purpura fulminans.

II) Extravascular causes

Purpura simplex: Appears in healthy women, usually about the time of menstruation, as easy bruising (Devil's pinches).

Senile purpura: Appears on the dorsa of the forearms and hands of the elderly. Prolonged topical fluorinated steroids or ingestion of steroids may produce also such lesions.

Scurvy (ascorbic acid deficiency): There is decrease in collagen polypeptides synthesis through a decrease in proline hydroxylation. Clinically, there is perifollicular petechiae on the lower extremities, "Corkscrew hairs", and follicular hyperkeratosis. Bleeding and friable gums occur in long-standing cases.

Autoerythrocyte sensitization syndrome "Painful-bruising syndrome"

It occurs commonly in women with hysterical personality, as recurrent attacks of red, raised, tender, painful areas of ecchymoses. The diagnosis is confirmed by intradermal injections of patient's sonicate RBCs. It is due to allergic sensitivity to RBCs in the tissues where minor extravasation of blood is followed by intense inflammatory reaction.

Neonatal purpura

Neonatal purpura (NP) should always be considered as an emergency.

Blueberry muffin baby "Dermal hematopoiesis"

Extramedullary hematopoiesis (EMH) is most commonly seen in neonates secondary to underlying bone marrow dysfunction. It may occur in adults with myeloproliferative disorders such as myelofibrosis or after splenectomy.

The skin eruption consists of dark-blue non-blanchable, small round to oval papules and nodules mainly on the head (Fig. 7), neck and trunk that spontaneously involutes in 2-6 weeks.

Causes of NP

- **Extramedullary erythropoiesis**
"Blueberry muffin baby".
- **Coagulation defects:**
 - Protein S and C deficiency "NP fulminans".
 - Hemorrhagic disease of the newborn.
 - Hereditary clotting factor deficiency.
- **Platelet abnormalities:**
 - Immune platelet destruction:
 - Alloimmune neonatal thrombocytopenia.
 - Maternal autoimmune thrombocytopenia (ITP, Lupus).
 - Drug-related.
 - Kasabach-Merritt syndrome.
 - Tryptophan production/function defect "rare".
- **Infections:** Congenital (TORCH), sepsis, HIV, parvovirus B19.
- **Trauma of delivery.**



Fig. 7. Blueberry muffin baby

Causes of blueberry muffin baby

1. **Persistence of dermal erythropoiesis** (that normally stops around 5th month with start of fetal myeloid differentiation). It represents a response to an increased demand for RBCs in infants with chronic anemia or a response to viral infection:

- Congenital infections:
 - Rubella.
 - CMV "main cause nowadays".
 - Parvovirus B19.
- Hemolytic disease of newborn:
 - Rh incompatibility.
 - Blood group incompatibility.
- Hereditary spherocytosis.
- Twin transfusion syndrome.

Most common associations are TORCH infections in neonates and myelofibrosis in adults.

2. **Neoplastic infiltrative diseases:**

e.g. Neuroblastoma, rhabdomyosarcoma, Langerhans cell histiocytosis and congenital leukemia.

Laboratory evaluation: CBP, Hb level, TORCH serologies (Toxoplasmosis, Other, Rubella, Cytomegalovirus & Herpes) viral cultures, Coomb's test.

Purpura pigmentosa chronica (capillaritis of unknown cause) ¹

A group of chronic asymptomatic dermatoses of unknown etiology with similar clinical and histopathological features, and not associated with an underlying systemic abnormality.

Pathogenesis: It is a T-cell mediated immune response due to:

- The infiltrate consisted mainly of CD3⁺, CD4⁺, CD36⁺ cell.
- LGs have been found in large amounts in the infiltrate.
- There is ↑ expression of adhesion molecules, e.g. ICAM1, ELAM1 and LFA1 in PPD.

NB: Certain drugs as carbromal and phenacetin may cause a clinical picture simulating itching purpura or Schamberg's disease.

Clinically (Fig. 8): These dermatoses are characterized by patches of purpuric puncta with orange or brown pigmentation as a result of hemosiderin deposits and telangiectasia as a result of capillary dilatation. The condition usually occurs on the lower extremities of adults, but may be extensive and may also occur in children. There are no systemic symptoms.

Histopathology (Figs 9-11): The capillaries of the upper dermis show swelling of their endothelial cells and are surrounded by extravasated erythrocytes and a lymphocytic infiltrate. Varying amounts of hemosiderin may be found. There is no evidence of vasculitis. The extent of vascular damage is usually mild & often insufficient to justify the term vasculitis, so vasculopathy is better.



Fig. 8. Purpura pigmentosa chronica

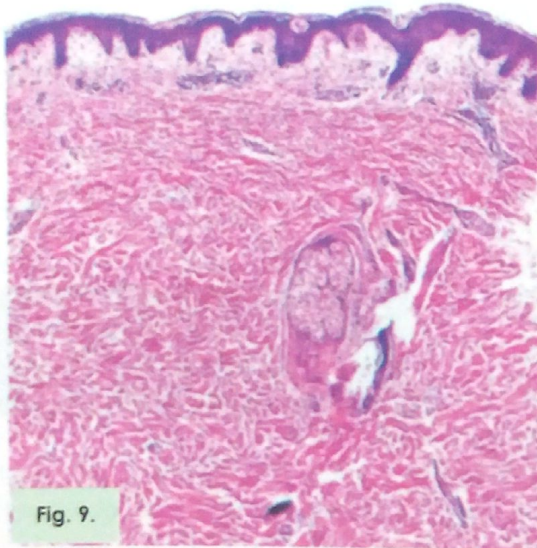


Fig. 9.

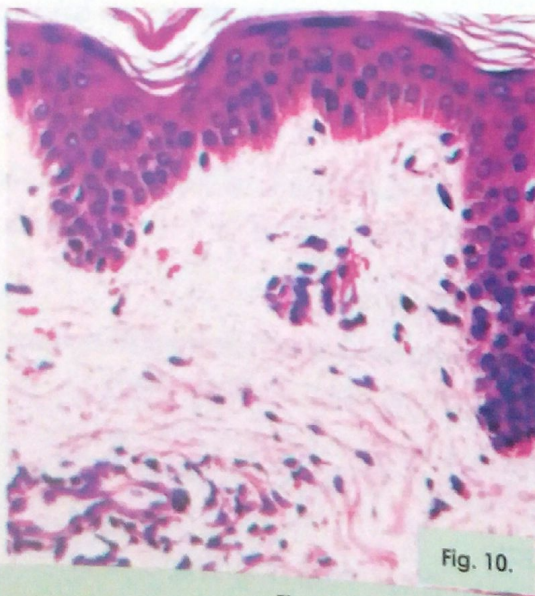


Fig. 10.

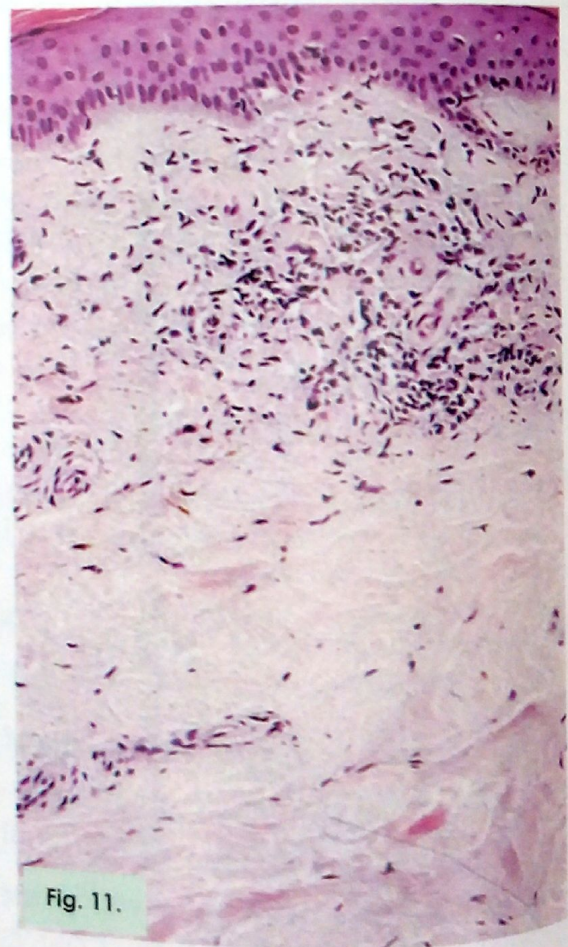


Fig. 11.

Figs 9-11. Histopathology of purpura pigmentosa chronica

5 dermatoses are known:

1. **Progressive pigmented purpuric dermatosis (Schamberg's disease)** (Figs 12-14): It is the most common type, more in young adult males. It is characterized by orange or brown macules and patches with erythematous non palpable puncta "cayenne pepper" spots within or on their borders. It is very chronic, but spontaneous cure may occur.



Figs 12-14. Schamberg's disease

2. **Pigmented purpuric lichenoid dermatosis of Gougerot & Blum:** More in older men (40-60 yrs). It is characterized by lichenoid papules in association with the purpuric lesions.
3. **Purpura annularis telangiectodes (Majocchi's disease):** More in young adults of either sex. It may occur at any site as brownish-yellow macular and annular lesions that may contain "cayenne pepper" spots and telangiectasia. Central clearing with slight atrophy may occur.
4. **Eczematid-like purpura of Doucas and Kapetanakis (itching purpura):** More in adult males. It is characterized by extremely pruritic erythematous and purpuric macules. Lichenoid papules may be scaly and become lichenified from scratching. It is usually localized to the legs but may be disseminated. Histologic examination shows, in addition to capillarities, epidermal changes as spongiosis.
5. **Lichen aureus:** Can be considered as a variant of purpura pigmentosa chronica with similar pathological changes (may be with a Grenz zone). It is characterized by rust-yellow patches, sometimes with petechiae, commonly located on the lower legs.
There are some cases of familial purpuric eruption (AD) occurring mainly in childhood or adolescence. Individual macules are larger and arranged in a mosaic pattern.

	Schamberg's disease	Itching purpura	Pigmented purpuric lichenoid dermatosis	Purpura annularis telangiectodes	Lichen aureus
Average age	40	40-50	40-60	30	30-40
Children	+	+	-	+	+
Sex	M>F	M>F	M>F	F>M	M>F
Primary lesion	Brown patches with "Cayenne pepper" puncta.	Pruritic purpuric macules with scales.	Purpuric papules with scales.	Purpuric annular plaque with atrophic center.	Golden lichenoid papules.
Distribution "mostly"	Legs.	Legs, arms, trunk & sites of friction.	Legs, arms & trunk, bilateral.	Legs, bilateral.	Legs, more unilateral.

Treatment of PPD

- Oral & topical steroid.
- Pentoxifylline has been tried.
- PUVA is effective in case of PPD of Gougerot-Blum variety.
- Griseofulvin may act as immunomodulator drug.
- Ascorbic acid (500 mg twice daily) plus rutoside (50 mg twice daily).

Microvascular occlusion syndromes

- It is critical to distinguish between inflammatory injury and non-inflammatory occlusive injury to vessels because the therapies for inflammatory disease differ greatly from therapies for occlusive disease. The use of anti-inflammatory therapy for occlusive disease may not only be useless but also harmful, and the same may be true for anticoagulant therapy in most vasculitides.
- The diagnosis of occlusive syndromes in the skin is greatly facilitated by finding the telltale lesions of **retiform purpura**.

Diagnosis of cutaneous microvascular occlusion based on pathophysiology

Platelet plugging

- Heparin necrosis*.
- Thrombocytosis secondary to myeloproliferative disorders.
- Paroxysmal nocturnal hemoglobinuria.
- Thrombotic thrombocytopenic purpura (rare).

Cold-related gelling or agglutination

- Cryoglobulinemia.
- Cryofibrinogenemia.
- Cold agglutinins.

Vessel-invasive organisms

- Ecthyma gangrenosum (primarily gram-negative bacteria).
- Opportunistic fungi (e.g. *Aspergillus* spp., *Rhizopus* spp.).
- Disseminated strongyloidiasis.
- Lucio's phenomenon of leprosy.

Embolization

- Cholesterol embolus.
- Oxalate embolus.
- Atrial myxoma.
- Marantic endocarditis.
- Libman-Sacks endocarditis (lupus, often in association with antiphospholipid antibodies).
- Infective endocarditis (acute, fungal) (rare)†.
- Crystalglobulin vasculopathy.
- Hypereosinophilic syndrome.

Systemic coagulopathies

- Neonatal purpura fulminans.
- Warfarin (Coumadin) necrosis.
- Purpura fulminans of sepsis/DIC.
- Postinfectious purpura fulminans.
- Antiphospholipid antibody/lupus anticoagulant syndrome.

Vascular coagulopathies

- Sheddson syndrome.
- Livedoid vasculopathy.
- "Malignant" atrophic papulosis.

Cell occlusion syndromes

- Stress reticulocyte adhesion with major hemolytic anemias &/or sickling.
- Intravascular lymphoma.

Miscellaneous/unknown mechanism

- Cutaneous calciphylaxis.
- Hydroxyurea-induced ulcers.
- Brown recluse (*Loxosceles*) spider bite.
- Local interferon injection reaction.
- Large hematoma occlusion syndrome.

* Encompasses heparin-induced thrombocytopenia (HIT)/heparin-associated thrombocytopenia & thrombosis (HATT).

† Usually inflammatory.

Cutaneous Vasculitis



- Cutaneous signs of vasculitis are a reflection of the size of the vessels involved.
- Vasculitis can be limited to the small vessels of the skin or it can be a sign of life-threatening internal organ involvement.
- The clinical diagnosis of cutaneous vasculitis requires histopathologic confirmation and multiple biopsies may be required.

Cutaneous leukocytoclastic vasculitis

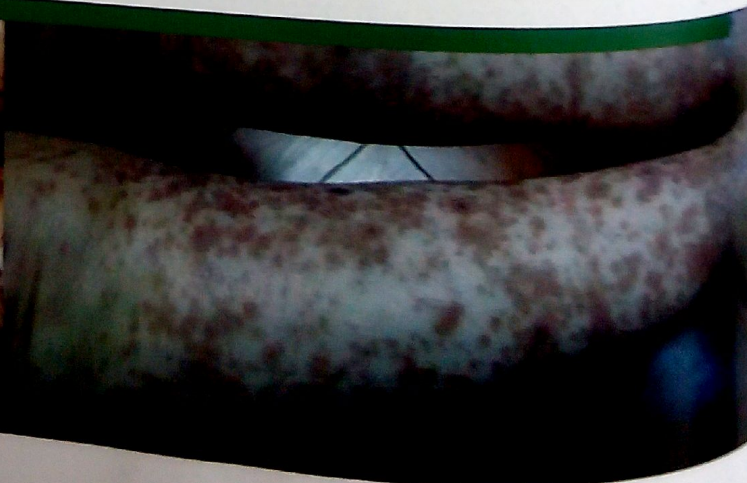
- Palpable purpura, urticarial lesions, hemorrhagic macules or vesicles.
- Lesions favor the lower extremities (especially the ankles), dependent areas or pressure points.
- Only involves small vessels (primarily postcapillary venules).
- Histopathologically, leukocytoclastic vasculitis is seen.
- Extracutaneous involvement occurs, but it is uncommon and usually mild.

ANCA-Associated Vasculitides

- The ANCA-associated vasculitides are characterized by involvement of small to medium-sized vessels, the presence of antineutrophil cytoplasmic antibodies (ANCA), and an overlapping spectrum of organ involvement, but with each having distinguishing clinical and laboratory features.
- The main three ANCA-associated vasculitides are: Microscopic polyangiitis (MPA), Wegener's granulomatosis and Churg-Strauss syndrome.

Cryoglobulinemic Vasculitis

- Palpable purpura, typically on the lower extremities.
- Myalgias and arthralgias.
- Associated with mixed serum cryoglobulins (IgM and IgG), most commonly in the setting of HCV infection.
- Peripheral neuropathy and glomerulonephritis can develop.



Vasculitis²

Vasculitis is inflammation of the blood vessels. Vascular syndromes are multisystem disorders which frequently involve organ systems with the richest vascular supply, such as the skin.

There are several classifications of vasculitis; the most accepted scheme is based on the size of the involved blood vessels. Subclassification is based on clinical and histological criteria.

Cutaneous vasculitis classification scheme

Caliber of the predominantly affected vessel	Classification	Subclassification or etiologies	Morphology of cutaneous lesions
Small	Cutaneous small vessel vasculitis (CSVV)	• Henoch-Schönlein purpura. • Acute hemorrhagic edema of infancy. • Urticarial vasculitis. • Erythema elevatum diutinum. • 2ry causes of CSVV: Drug exposure, infections, malignancies "most often hematologic".	• Palpable purpura (most common). • Other: Petechiae, macular purpura, urticarial papules, vesicles, pustules, targetoid papules & plaques.
Small & medium-sized "mixed"	Cryoglobulinemia	• Types II & III.	• Petechiae. • Palpable purpura. • Livedo racemosa. • Retiform purpura. • Ulcers. • Subcutaneous nodules. • Digital necrosis.
	ANCA-associated	• Microscopic polyangiitis. • Wegener's granulomatosis. • Churg-Strauss syndrome.	
	2ry causes	• Infections. • Inflammatory disorders (e.g. AI-CTD).	
Medium-sized	Polyarteritis nodosa (PAN)	• Classic (systemic) PAN. • Cutaneous PAN.	• Livedo racemosa. • Retiform purpura. • Ulcers. • Subcutaneous nodules. • Digital necrosis.
Large*	Temporal arteritis		• Early – erythematous or cyanotic skin, alopecia, purpura, tender nodules on frontotemporal scalp. • Late – Ulceration &/or gangrene of frontotemporal scalp or tongue.
	Takayasu's arteritis		• Erythematous subcutaneous nodules + ulceration, pyoderma gangrenosum-like lesions on the extremities (lower > upper). • May have evidence of small &/or medium-sized vessel vasculitis.

* Cutaneous manifestations are rare.

It is useful to divide vasculitis syndromes into two groups:

1. **Immune complex vasculitis:** Usually dependent distribution.
 - Predominant IgG, IgM: Idiopathic, drugs, infection.
 - Predominant IgA: Idiopathic, HSP, drugs, infection.
 - Benign hypergammaglobulinemic purpura of Waldenström.
 - Some pustular vasculitis.
 - Mixed cryoglobulinemia.
 - Rheumatic vasculitides: SLE, RA, DM.
2. **Non-immune complex (pauci-immune vasculitis):** Usually random distribution.
 - ANCA-associated
 - Wegener's.
 - Microscopic PA.
 - Churg-Strauss
 - Non-ANCA-associated
 - EED.
 - Granuloma faciale.
 - Sweet's.
 - Some pustular vasculitis.
 - Benign cutaneous PAN.

Cutaneous small-vessel vasculitis (CSVV)²

"Leukocytoclastic vasculitis – Necrotizing vasculitis – Hypersensitivity vasculitis"

CSVV refers to a group of disorders characterized clinically mainly by palpable purpura on the skin and pathologically by leukocytoclastic vasculitis of postcapillary venules & fibrinoid necrosis. CSVV can be idiopathic or can be associated with a drug, infection or underlying systemic disease. Initially, the pathogenesis is immune complex related, but in its later stages different pathogenetic mechanisms may intensify the reaction. Systemic vascular involvement may occur, mainly in the kidneys, muscles, joints, GIT and peripheral nerves.

Henoch-Schönlein purpura is a type of CSVV mediated by IgA immune complexes.

Epidemiology: It occurs equally in both sexes and at all ages.

Clinical features (Figs 15-26)

- There is a spectrum of cutaneous lesions, although palpable purpura is its hallmark. At the onset, the lesions may not be palpable but almost all patients have purpura. As the process continues, the lesions may become papulonodular, vesicular, bullous, pustular or ulcerated. Lesions, usually at the same stage, occur in crops mainly on the legs & ankles. Other pressure sites may be affected. Uncommon sites are face, palms, soles and mucous membranes.

The ACR classification criteria for Hypersensitivity vasculitis (HSV)

- Age >16 yrs at onset.
- Medications that may have precipitated event.
- Palpable purpura.
- Cutaneous eruption.
- Positive biopsy results.
- Three criteria classify HSV with sensitivity of 71.0% & specificity of 83.9%.



Fig. 15.



Fig. 16.



Fig. 17.



Fig. 18.



Fig. 19.



Fig. 20.



Fig. 21.



Fig. 22.

Figs. 15-22. Leukocytoclastic vasculitis



Fig. 23. Leukocytoclastic vasculitis



Fig. 24. Leukocytoclastic vasculitis



Fig. 25. Leukocytoclastic vasculitis



Fig. 26. Hypersensitivity vasculitis

- Lesions may be mildly purpuric or painful & subside within 3 or 4 weeks leaving residual hyperpigmentation or atrophic scars.
- Fever, malaise, arthralgia and/or myalgia may occur.
- The disease may be self-limiting but can recur or become chronic and intermittent.

Chronicity is predicted by:

- Arthralgias.
- Cryoglobulinemia.
- Absence of fever.

Etiological factors

1. **Idiopathic (45-55%):** No cause can be identified.

2. Infections (15-20%):

- **Bacterial infections** (β hemolytic streptococcus group A, staphylococcus aureus, mycobacterium leprae).
- **Viral infections** (hepatitis A, B, C virus; herpes simplex virus; influenza virus).
- **Fungal infections** (Candida albicans).
- **Protozoan infections** (Plasmodium malariae).
- **Helminthic infections** (Schistosoma hematobium, Schistosoma mansoni, Onchocerca volvulus).

3. Drugs and chemicals (10-15%):

Insulin, penicillin, hydantoins, streptomycin, aminosalicylic acid, thiazides, phenothiazines, vitamins, phenylbutazone, quinine, streptokinase, tamoxifen, anti-influenza vaccines, oral contraceptives & chemicals (insecticides, petroleum products).

4. Chronic diseases:

- CTDs, e.g. SLE, Sjögren's syndrome, Rheumatoid arthritis (15-20%).
- Behçet's disease.
- Hyperglobulinemic states.
- Cryoglobulinemia.
- Ulcerative colitis.
- Primary biliary cirrhosis.
- Cystic fibrosis.
- HIV seropositivity & AIDS.
- Bowel bypass syndrome.

5. Malignant neoplasms (5%):

- Lymphoproliferative disorders, e.g. Hodgkin's disease, mycosis fungoides.
- Cancers of lung, colon, renal, prostate and breast.

Mechanisms that explain the association of CSVV and malignancy

- Immunologic reaction against vascular endothelium.
- Release of various cytokines.
- Delayed hypersensitivity reaction by deposition of cancer proteins on vessel walls.
- Over-run vessel walls.
- Induce critical levels of circulating immune complex.
- Behave as sensitizing agents.

6. Other disorders, e.g.

- Henoch-Schönlein syndrome.
- Acute hemorrhagic edema of childhood.
- Urticarial vasculitis.
- Nodular vasculitis.
- Erythema elevatum diutinum.
- Livedoid vasculitis.

Systemic involvement in CSVV

- Any organ can be involved with associated specific clinical and pathologic manifestations: pleura, pericardium, synovia and GIT are frequently affected.
- Systemic vasculitis often, but not always, has cutaneous manifestations.

Systemic manifestations

- **Kidneys** (nephritis with microscopic hematuria and proteinuria; acute & chronic renal failure).
- **Gastrointestinal tract** (colicky pain, nausea, vomiting, diarrhea, melena and hematemesis).
- **Lungs** (asymptomatic or cough and hemoptysis).

2

Hallmarks of cutaneous small vessel vasculitis

- **Clinical:** Palpable purpura.
- **Histopathologic:** Leukocytoclastic vasculitis.
- **Electron microscopic:** Postcapillary venule.
- **Mechanism:** Circulating immune complex-mediated, neutrophil-induced vessel damage, adhesion molecules.

- **Heart** (myocardial angitis, pericarditis).
- **Nervous system** (headache, diplopia, hypoesthesia, paraesthesia).
- **Joints** (arthralgia, arthritis).
- **Ear, nose and throat** (particularly in granulomatous vasculitis).
- **Eyes** (retinal vasculitis, conjunctivitis, keratitis, pseudotumor cerebri).
- **Miscellaneous** (fever, constitutional symptoms, pancreatitis).

Histopathology (Figs 27-29)

- It is characterized by **leukocytoclastic vasculitis**: Angiocentric segmental inflammation, endothelial cell swelling, fibrinoid necrosis of blood vessel wall (post-capillary vessels) and cellular infiltrate around and within dermal blood vessel walls composed largely of neutrophils with fragmented nuclei (karyorrhexis or leukocytoclasia) and extravasation of erythrocytes.
- Thrombosis of the affected post-capillary venules and hyalinization of blood vessel wall may be observed in late phase of the disease.
- Lymphocytes and monocytes may predominate in the infiltrate in late stages.

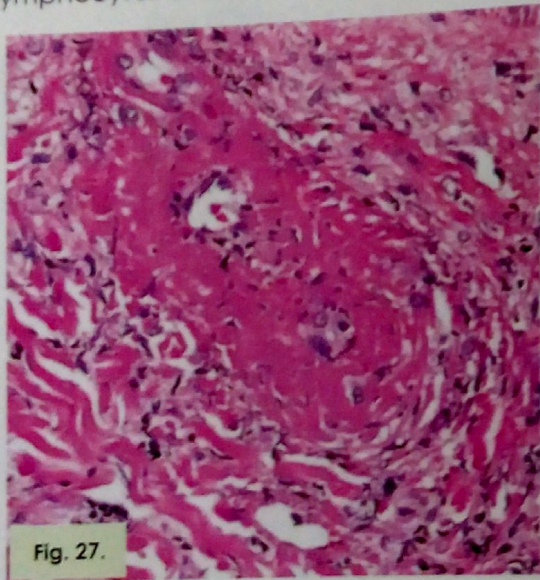


Fig. 27.

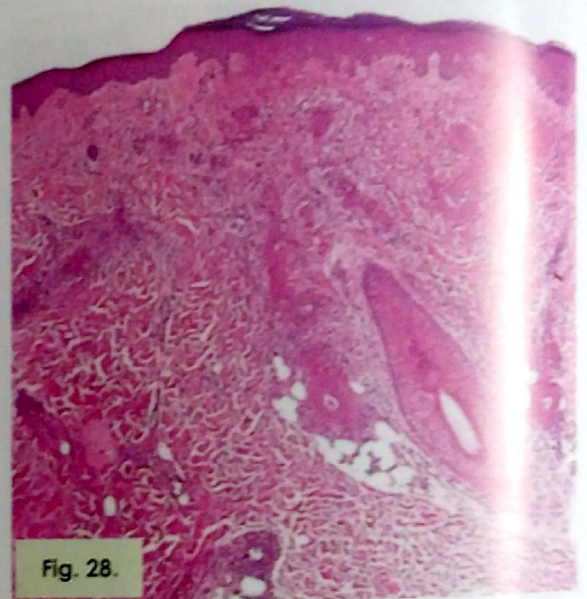


Fig. 28.

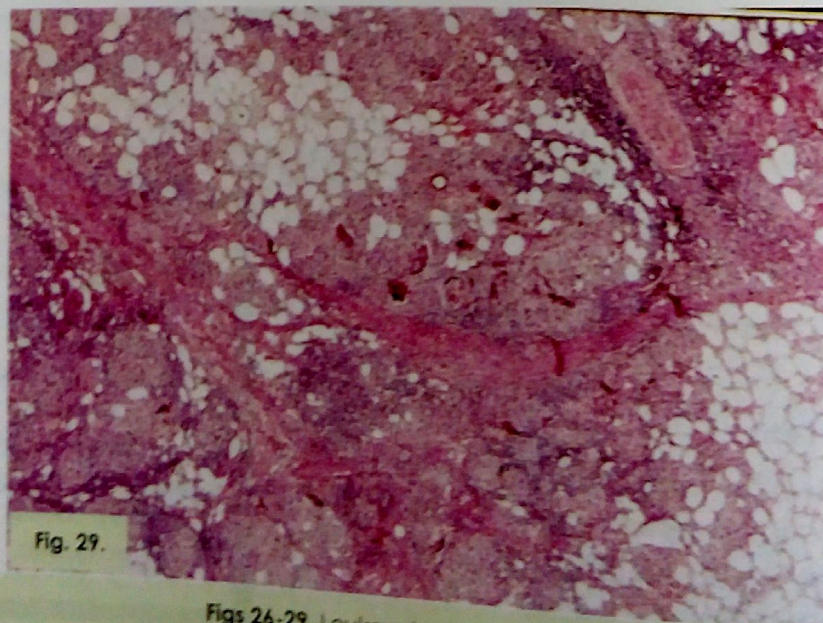


Fig. 29.

Figs 26-29. Leukocytoclastic vasculitis

There are many factors that appear to influence the deposition of circulating immune complexes and both amplify and maintain the tissue damage, including:

- The ability of erythrocytes to transport complement-related immune complex to the fixed macrophage system.
- The hydrostatic pressure and turbulent flow.
- The functional state of the macrophage system.
- Release of various mediators from the platelet.
- The integrity of the fibrinolytic system: cutaneous fibrinolytic activity varies depending on the stage of the disease. It is increased in early phase and reduced in late phase.

DIF: Immunoglobulins (IgG, IgM, IgA), complement (C1 q, C3), fibrin deposits within post-capillary venular wall.

Dynamic nature of CSVV: The infiltrate progressively changes from a predominance of neutrophils over lymphocytes to a predominance of lymphocytes as a continuum of a single disease process.

- Abnormal fibrinolysis has been found in patients with CSVV. Circulating immune complexes interacting by means of their FC receptor with venular endothelial cells may determine in the first stage of the disease (hyperfibrinolytic phase) a massive release of endothelial tissue-type plasminogen activator (t-PA). This hyperfibrinolytic phase is manifested clinically by urticarial wheals. This is followed by late hyperfibrinolytic phase as a result of reduction of t-PA leading to intravascular deposition of fibrin. This phase is manifested clinically by palpable purpura.
- Neuropeptides modulate the fibrinolytic system, local immune system and activate macrophages and mast cells. Also, induce expression of adhesion molecules.
- Gamma / Delta lymphocytes and human heat shock proteins (HSPs) are strongly represented only in lesional skin in cases of leukocytoclastic vasculitis of documented infectious cause.

Treatment (Fig. 30)

First-line treatment:

- Identification and removal of the causative agent.
- Supportive care.
- Symptomatic relief: NSAIDs and antihistamines.

Second-line treatment:

- Colchicine (0.6 mg bid-tid).
- Dapsone (50-200 mg/day).
- Systemic steroid (60-80 mg/day).
- Hydroxychloroquine.

Third-line treatment:

- Immunosuppressive agents such as azathioprine 100-200 mg/day (2 mg/kg/day) & methotrexate (<25 mg weekly).
- IVIGs.
- Plasmapheresis.
- Monoclonal antibody treatment against ICAM-1 or VCAM-1 in intractable systemic vasculitis.



Fig. 30. CSVV before and after treatment

Henoch-Schönlein Purpura "HSP" (Anaphylactoid purpura)²

HSP is the most common form of vasculitis in children. It is an IgA-mediated small-vessel vasculitis that affects skin, joints, GIT and kidneys.

Epidemiology

It occurs primarily in male children between 2-11 years, occurring more in spring and winter. It usually follows upper respiratory tract streptococcal infections in 60-75% of patients.

Clinical picture (PAPAH)

- **Palpable purpura (100%):** Symmetric petechial hemorrhagic or palpable purpuric lesions on the lower extremities and buttocks. It regresses after 10-14 days.
- **Abdominal Pain GIT (61-67%):** Colicky pain, vomiting, melena and hematemesis.
- **Arthralgias and arthritis (74-84%):** Usually involves the knee and ankles.
- **Renal changes (44-47%):** Acute focal or diffuse glomerulonephritis → Hematuria.

Progression to acute or chronic renal failure may occur.

The American college of Rheumatology (1990) criteria for classification of HSP

Criterion	Definition
Palpable purpura	Slightly raised palpable hemorrhagic skin lesions, not related to thrombocytopenia.
Age ≤20 yrs at disease onset	Patient 20 yrs of age or younger at onset of first symptoms.
Bowel angina	Diffuse abdominal pain, worse after meals or the diagnosis of bowel ischemia, usually including bloody diarrhea.
Vessel wall granulocytes on biopsy	Histologic changes showing granulocytes in the walls of arterioles or venules.

The presence of any two or more criteria yields a sensitivity of 87.1% & a specificity of 87.7%.

The condition lasts about 2-4 weeks, but recurrence occurs in 40% of cases. Death occurs in some patients from renal failure.

DIF: IgA, C3 and fibrinogen within vessel walls.

Pathogenesis

IgA immune complexes deposited in the affected organs and activate alternative pathway of complement → formation of membrane attack complex of complement → chemotactic factors and leukocytoclastic vasculitis with depletion of factor XIII leading to further bleeding and fibrin deposition. The responsible antigen is usually an infectious agent.

Treatment

First-line treatment:

- Supportive care (bed rest).
- NSAIDs for arthralgia.

Second-line treatment:

- Dapsone and colchicine may decrease the duration of cutaneous lesions.
- Systemic corticosteroids: Treat arthritis and abdominal pain and reduce the duration of skin lesions, but do not prevent recurrences of purpura. Corticosteroids do not prevent renal disease but could be used to treat severe nephritis.
- Azathioprine ± Systemic corticosteroids.

Third-line treatment:

- IVIg.
- Rituximab.
- Mycophenolate mofetil.
- Systemic corticosteroids + tacrolimus.
- Plasma exchange (rapidly progressive GN).

Poor prognostic factors of HSP

- Renal failure at the time of onset.
- Nephrotic syndrome.
- Hypertension.
- Decreased factor XIII activity.

IgA vasculitis: Vasculitis and vascular IgA deposition

- Henoch-Schönlein purpura / IgA vasculitis.
- Mixed cryoglobulinemia.
- Rheumatic vasculitis, especially SLE.
- Livedoid vasculopathy? (vasculopathy)?

The ACR classification criteria for Henoch-Schönlein purpura (HSP):

- Palpable purpura
- Age at onset <20 y
- Bowel angina.
- Vessel wall granulocytes on biopsy.

Two criteria classify HSP with sensitivity of 87% & specificity of 88%.

HSP should be differentiated from acute hemorrhagic edema (AHE)

Common features	AHE	HSP
Sex	Slight male predominance.	
Season	Cold season.	
Prodromes	Respiratory infection, drug intake, immunization.	
Inflammatory syndrome	Frequent	
Distinctive features		
Age	4-24 months.	Peak 3-7 years.
Purpura	Ecchymotic cockade pattern; limbs & face.	Papulopetechial, urticarial lesions, predominantly on lower limbs.
Edema	Constant, often extensive	Inconstant
Visceral involvement	Very uncommon	Frequent
Histopathology:		
• Leukocytoclastic vasculitis	• +	• + (often less marked).
• Fibrinoid necrosis	• Frequent	• Uncommon.
Direct immunofluorescence (perivascular IgA deposits)	Often negative	+
Mean duration (days)	12	30
Relapse	None	Frequent

Hypersensitivity angitis

It is the most severe form of vasculitis characterized by marked pulmonary & renal involvement.

Death occurs within few days or weeks usually from renal failure.

Urticarial vasculitis syndrome "UVS"¹

Urticarial vasculitis is a clinicopathologic entity consisting of persistent urticarial lesions that demonstrate the histopathologic features of leukocytoclastic vasculitis.

Epidemiology

Age: 30-50 years.

Sex: Female: male (3 : 1).

Etiology

- Idiopathic.
- Collagen vascular diseases, e.g. SLE.
- Serum sickness.
- Infections, e.g. hepatitis B.
- Drugs e.g. potassium iodide, fluoxetine and NSAIDs.
- Benign and malignant hematologic disorders (e.g. IgM or IgG monoclonal gammopathies, IgA multiple myeloma).

Pathogenesis

Pathogenesis of urticarial vasculitis is similar to that of typical CSVV (complement activation triggers mast cell release of inflammatory mediators, e.g. TNF- α that in turn increase the expression

of ICAM on mast cells "important for eosinophil transmigration" and E-selectin on endothelial cells).

Clinical picture (Figs 31-35)

- It is a chronic multisystem disease characterized by recurrent episodes of urticarial wheals that persist >24 hrs. (generally 3-4 days), often reveal purpura on blanching. Unlike ordinary urticaria, it is painful rather than pruritic and it resolves with residual hyperpigmentation (hemosiderin deposition).
- It is often associated with arthralgia, abdominal pain, uveitis, low-grade fever and glomerulonephritis.



Fig. 31.



Fig. 32.



Fig. 33.



Fig. 34.



Fig. 35.

Figs 31-35. Urticarial vasculitis

The disease spectrum

- **Normocomplementemic cases:** Skin-limited disease.
- **Hypocomplementemic urticarial vasculitis:** Patients with urticarial vasculitis & hypocomplementemia who do not meet the criteria for hypocomplementemic urticarial vasculitis syndrome.
- **Hypocomplementemic urticarial vasculitis syndrome (HUVS):** The more severe end of the disease spectrum. It is defined by:

2 major criteria:

- Urticaria for 6 months.
- Hypocomplementemia

+

2 minor criteria:

- Vasculitis on skin biopsy.
- Arthralgia or arthritis.
- Uveitis or episcleritis.
- Glomerulonephritis.
- Recurrent abdominal pain, or
- Positive C1q precipitin test with a low C1q level.

HUVS shares features with SLE, but distinctive clinical findings in HUVS include ocular inflammation (30%; conjunctivitis, episcleritis, iritis, uveitis), angioedema (>50%), & COPD-like symptoms (50%).

NB: Schnitzler's syndrome: Urticarial vasculitis + monoclonal IgM gammopathy + at least 2 of the following: Fever, arthralgias, hepatosplenomegaly, ↑ ESR, ↑ WBC, bone abnormality, bone pain).

Dermatopathology (Fig. 36): Leukocytoclastic vasculitis.

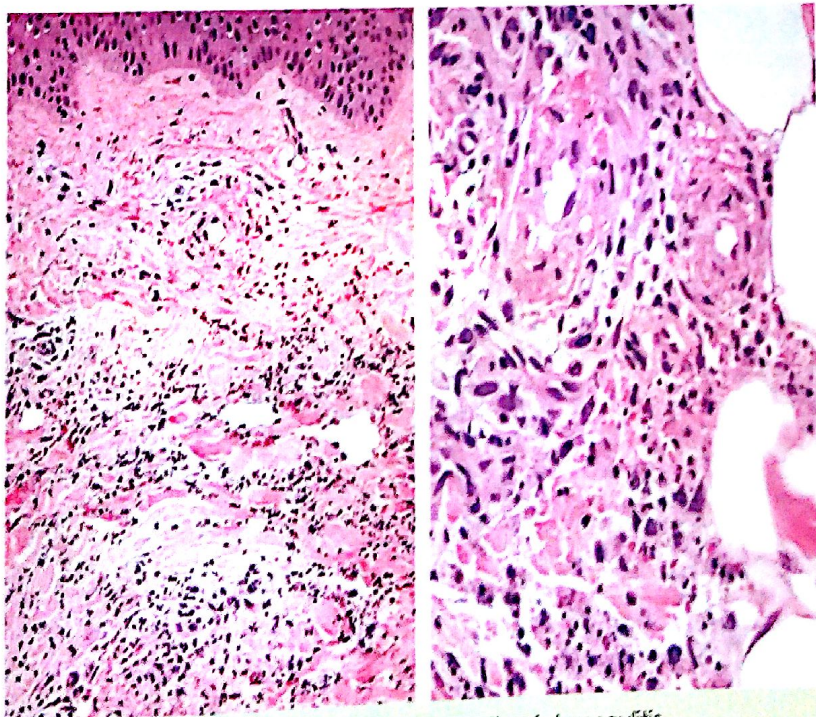


Fig. 36. Histopathology of urticarial vasculitis

Laboratory examination: ↑ ESR, hypocomplementemia (70%), circulating immune complexes.

Treatment: Exclude vascular or connective tissue disease.

1st line:

- H1 & H2 antihistamines (Chlorphenoxamine "Allergex[®]" or the non-sedating 3rd generation antihistamines Fexofenadine "Telfast[®]" 180 mg) and cimetidine "Tagamet[®]" or Ranitidine "Zantac[®]".
- NSAIDs, e.g. Indomethacin "Indocid[®]", Ibuprofen "Brufen[®]".
- Dapsone (100-200 mg/day) ± pentoxifylline.
- Corticosteroids.

2nd line:

- Colchicine 6 mg bid or tid.
- Hydroxychloroquine (200-400 mg/day).
- Azathioprine or methotrexate.

3rd line:

- Mycophenolate mofetil.
- IVIg.
- Rituximab.
- Cyclosporine.
- Plasmapheresis.

Systemic rheumatoid vasculitis

It may occur in patients with severe long-standing rheumatoid arthritis associated with high titers of rheumatoid factor. Cutaneous lesions include: Subcutaneous rheumatoid nodules, cutaneous ulcers, digital infarcts, purpuric lesions. The condition may be fatal due to cardiac, pulmonary or renal affection.

Lymphocytic Vasculitis

Pityriasis Lichenoides ①

Pityriasis lichenoides et varioliformis acuta (PLEVA) and pityriasis lichenoides chronica (PLC) are two ends of a disease spectrum.

Pathogenesis

- The etiology is unknown.
- Response to foreign antigens: Infections (HIV) – drugs (chemotherapeutic drugs, or estrogen-progesterone therapy).
- Predominance of CD8+ cells in PLEVA and CD4+ cells in PLC.
- Lesions exhibit dominant T-cell clonality, and so it can be considered as a T-cell lymphoproliferative disorder.

1. **Pityriasis lichenoides et varioliformis acuta "PLEVA":** It occurs commonly in young adults, mainly on the trunk. There is abrupt onset of crops of extensive erythematous papules which undergo central vesiculation and may be hemorrhagic necrosis. Rupture of lesions usually leave reddish-brown crusts which soon separate leaving small depressed scars. Severe necrosis may occur and heal with atrophic scars. There is continuous development of new lesions over several months. An infective agent possibly Epstein-Barr virus or toxoplasma may be responsible.

Febrile ulceronecrotic Mucha-Habermann disease (FUMHD): It is a severe variant of PLEVA in which the acute skin lesions are associated with malaise, fever, lymphadenopathy, arthritis &/or bacteremia and mucosal (gastrointestinal and pulmonary) involvement.

Although PLEVA may occasionally progress to chronic pityriasis lichenoides, there is no transformation into a lymphoma.

Histopathology: Perivascular lymphocytic infiltrate extending into the epidermis. Epidermal spongiosis, intracellular edema and necrosis occur. Some RBCs are seen "trapped" within the epidermis. Vascular damage with fibrinoid necrosis occurs in few cases, which is against the view of being lymphocytic vasculitis.

2. **Pityriasis lichenoides chronica (PLC)** (Figs 37, 38): There are recurrent crops of brown-red papules, mainly on the trunk, covered with adherent scales which are detached by gentle scrapping "mica-like scales" to reveal shining brown surface. Slow healing occurs in 3-4 weeks leaving pigmented macules.



Fig. 37. Pityriasis lichenoides chronica

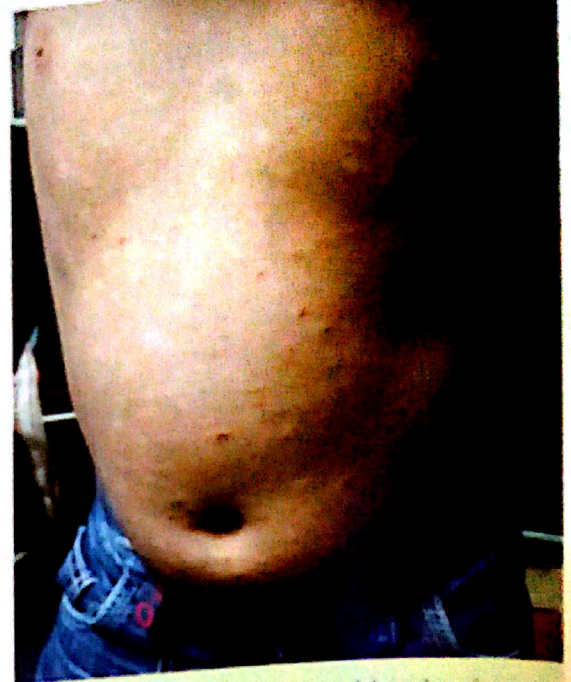


Fig. 38. Pityriasis lichenoides chronica

Histopathology: Epidermal alteration (spongiosis and parakeratosis) & a lymphocytic perivascular infiltrate.

Treatment:

- Antihistamines and topical corticosteroids.
- Topical coal tar preparations.
- Tetracycline, erythromycin: Used for their anti-inflammatory rather than antibiotic effects, with erythromycin favored in children.
- Various types of phototherapy.

More fulminant cases:

- Low-dose weekly methotrexate.
- Systemic corticosteroids.
- IVIg.
- Cyclosporine.
- Etanercept, oral bromelain (bromelin) and photodynamic therapy.

Comparison of features of lymphomatoid papulosis (LyP) and PLEVA

	LyP	PLEVA
Clinical features	Crops of recurrent necrotic papules & nodules on trunk & extremities.	Widely scattered recurrent papules with hemorrhagic crusts on trunk & extremities.
Duration	Protracted course over many years.	Generally weeks to months.
Histologic findings	• Prominent atypical cells: Large, multinucleated or small, cerebriform nucleus. • Neutrophils & eosinophils within lymphocytic infiltrate. • No epidermal dyskeratosis.	• Rare atypical cells. • Rare eosinophils. • Prominent epidermal dyskeratosis.
Immunohistochemistry	• CD4+ helper T-cells predominate. • CD7 antigen expression decreased. • Ki-1+/CD30+	• CD8+ cytotoxic/suppressor T-cells may predominate. • CD7 antigen expression normal. • Ki-1/CD30 absent.
Natural history	Progression to systemic lymphoma.	Rare, if any association with systemic lymphoma.

Vasculitis with granulomatosis

Systemic diseases in which necrotizing vasculitis is present in association with necrotizing granulomas. Treatment with cyclophosphamide and prednisone may induce remission.

Churg-Strauss syndrome is the rarest of the necrotizing vasculitides.

1) Allergic granulomatosis (Churg-Strauss syndrome)

Necrotizing granulomatous vasculitis + asthma + eosinophilia.

Pathogenesis

- Tissue infiltration and then degranulation of eosinophils leading to tissue injury.
- T-cells, especially Th2 cells contribute to granuloma formation.
- ANCA-dependent activation of neutrophils.

Triggering factors: Vaccination, desensitization therapy, leukotriene inhibitors & rapid discontinuation of corticosteroids.

Clinical features:

- **3 phases:**
 - **1st phase:** Allergic rhinitis, nasal polyps and asthma.
 - **2nd phase:** Peripheral eosinophilia, respiratory tract infections and gastrointestinal symptoms.
 - **3rd phase:** Systemic vasculitis with granulomatous inflammation.
- Cutaneous findings: During the 3rd phase of the disease. The most common skin lesions are palpable purpura, followed by subcutaneous nodules (typically on the scalp or extremities).
- Other systemic manifestations: Mononeuritis multiplex, granulomatous inflammation of the myocardium, necrotizing glomerulonephritis, musculoskeletal and ocular involvement.

Laboratory findings:

- Eosinophilia.
- ANCA 60% directed against MPO, 10-15% anti-PR3 ANCA.

The histologic hallmarks:

- Infiltrates of eosinophils.
- Formation of extravascular granulomas.
- Necrotizing vasculitis of small to medium-sized vessels.

Treatment:

- First-line: Systemic corticosteroid.
- Second-line treatment: Add cyclophosphamide in cases of internal organ involvement.

Churg-Strauss Syndrome "BEAN-SAP"

- Blood eosinophilia >10% (95%).
- Asthma (100%).
- Neuropathy (75%).
- Sinus abnormalities (86%).
- Allergies.
- Perivascular eosinophils (14%).

The ACR classification criteria for Churg-Strauss syndrome (CSS)

- Asthma.
- Eosinophilia (>10%).
- Neuropathy.
- Pulmonary infiltrates (nonfixed).
- Sinusitis.
- Extravascular eosinophils on biopsy.

Four criteria classify CSS with sensitivity of 85% and specificity of 99.7%.

• Third-line: IVIg $\pm$ plasmapheresis, Rituximab, azathioprine, methotrexate; mycophenolate mofetil, IFN- α .

2) Wegener's granulomatosis

Wegener's granulomatosis is classically described as the triad of: Granulomatous inflammation of the upper & lower respiratory tracts, systemic necrotizing small vessel vasculitis, and pauci-immune glomerulonephritis.

Pathogenesis

ANCA binding to PR3 on neutrophils results in vessel damage (e.g. pauci-immune or non-immune complex-mediated vasculitis).

Clinically

There may be urticarial, maculopapular or erythematous lesion. Pyoderma gangrenosum over neck, thigh and buttock is not uncommon in early stage. Peri-auricular lesion destroying the ear may be one of the earliest manifestations. Death occurs from renal failure.

Laboratory investigations

- Anemia and leukocytosis.
- $\uparrow$ ESR and CRP.
- C-ANCA +ve in about 80% of cases.

Treatment

- The standard treatment: Systemic corticosteroids (e.g. 1 mg/kg/day of prednisone) + oral daily cyclophosphamide.
- Other lines: Corticosteroids + Rituximab, mycophenolate mofetil, IVIg, plasmapheresis, methotrexate, azathioprine.

3) Lymphomatoid granulomatosis

Systemic manifestations: Respiratory tract manifestations, fever, arthralgias & neurologic abnormalities.

Cutaneous lesions (1/3 of patients): Erythematous papules, plaques and subcutaneous nodules with tendency to ulcerate. Progression into malignant lymphoma may occur. It is now believed that lymphomatoid granulomatosis is a lymphoma that at first evokes vasculitis.

4) Temporal (Giant cell) arteritis

It is a systemic granulomatous vasculitis of medium and large-sized arteries, most commonly the temporal artery in association with involvement of other cranial arteries, in particular retinal arteries. It is characterized by headache, fatigue, fever, claudication of jaw/tongue, anemia, sudden visual impairment and high ESR, in elderly patients.

Wegener's granulomatosis "ROUGH"

- R** Abnormal chest Radiograph.
- O** Oral ulcer or nasal discharge.
- U** Urinary sedimentation "abnormal".
- G** Granulomatous inflammation on biopsy.
- H** Hemoptysis.

The ACR classification criteria for vasculitis Wegener's granulomatosis (WG)

HL

- Nasal or oral inflammation.
- Chest X-ray showing nodules, infiltrates (fixed) or cavities.
- Microscopic hematuria or red cell casts in urine.
- Granulomatous inflammation on biopsy (within vessel wall or perivascular).

Two criteria classify WG with sensitivity of 88.2% & specificity of 92.0%.

Systemic vasculitis: Claudication of extremities, stroke, myocardial infarction, aortic aneurysm/dissections, visceral organ infarction.

Skin lesions: The superficial temporal arteries are prominent, tortuous, tender and pulseless. Erythema of overlying skin, gangrene and ulceration with exposure of bone.

Temporal artery biopsy: A pan mural predominantly mononuclear infiltrate with giant cells and fragmentation of elastic fibers.

Treatment:

- Prednisone: 40-60 mg/d.
- Methotrexate: 15-20 mg once weekly has a steroid-sparing effect.

The ACR classification criteria for giant cell (temporal) arteritis (GCA)

- Age >50 years at onset.
- New type of headache.
- Abnormal temporal artery on clinical examination (tenderness to palpation or decreased pulsation).
- Elevated erythrocyte sedimentation rate.
- Temporal artery biopsy showing vasculitis.

Three criteria classify GCA with sensitivity of 93.5% & specificity of 91.2%.

ANCA-associated vasculitides

The ANCA-associated vasculitides are characterized by:

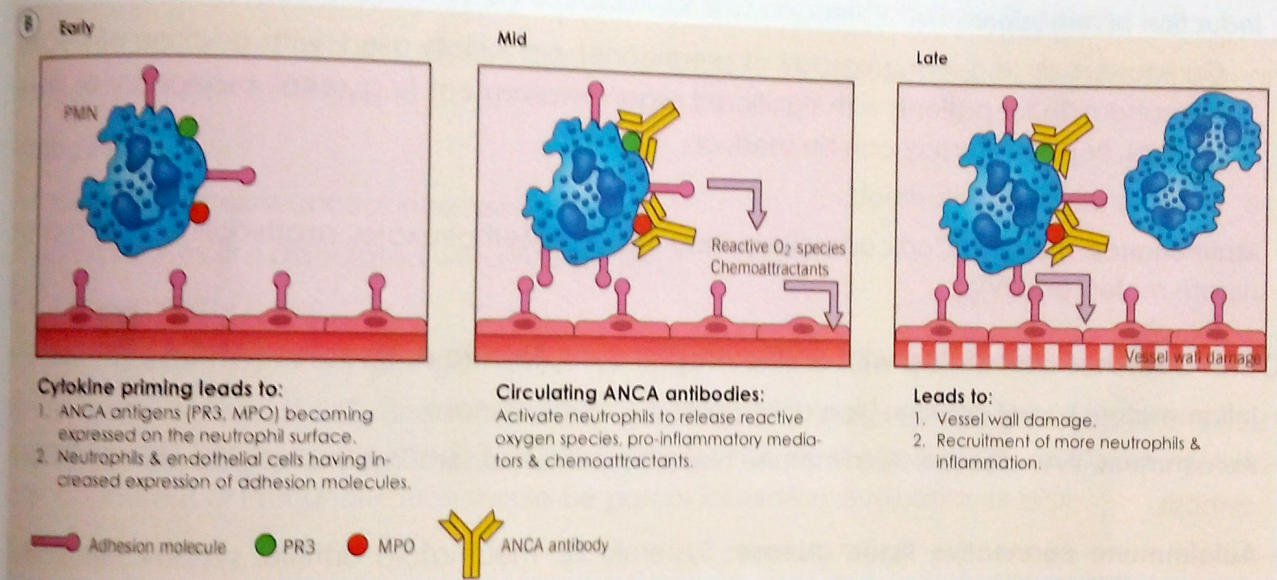
- Involvement of small to medium-sized vessels.
- The presence of antineutrophil cytoplasmic antibodies (ANCA).
- Overlapping spectrum of organ involvement.

Pathogenesis

ANCA: Anti-Neutrophil Cytoplasmic Antibodies should be done in every patient. Two patterns:

- A cytoplasmic pattern (c-ANCA) & a perinuclear pattern (p-ANCA). c-ANCA, which is directed against increased proteinase-3 (PR3), is increased in Wegener's granulomatosis (>90%), Wegener's granulomatosis without renal involvement (75%) and vasculitis overlap (40-50%).
- While (p-ANCA), which is directed against myeloperoxidase (MPO) is found in other forms of CSVV.

ANCA in vasculitis



Adapted mainly from: Bologna et al., *Dermatology Textbook*, Third edition, 2012.

The main three ANCA-associated vasculitides:

- Microscopic polyangiitis (MPA).
- Wegener's granulomatosis.
- Churg-Strauss syndrome.

Microscopic polyangiitis

Pathogenesis

- Triggering factors: Medications or malignancy.
- ANCA are thought to play a role in the pathogenesis.

Clinical features

- **Constitutional symptoms** (fever, weight loss, arthralgias and myalgias).

- **Cutaneous involvement:** Up to 70% of patients, most commonly palpable purpura, but may be erythematous patches, livedo racemosa, and splinter hemorrhages.
 - **Renal involvement (>90%):** Pauci-immune, crescentic, necrotizing glomerulonephritis may lead to renal failure.
 - **Pulmonary capillaritis (30-50%):** Dyspnea and pulmonary infiltrates which can result in diffuse alveolar hemorrhage.
 - **Neurologic involvement:** Peripheral neuropathy or mononeuritis multiplex.
- Laboratory:** Anti-MPO antibodies occur in 60% of patients, while anti-PR3 antibodies can be seen in 30% of cases.

Pathology

- Segmental necrotizing vasculitis of the smallest blood vessels.
- Vasculitis of small and/or medium-sized arteries.
- No granulomatous inflammation.

Treatment

- **Induction of remission:**
 - Corticosteroids (e.g. 1 mg/kg/day of prednisone) are initially used, with addition of cyclophosphamide for patients with significant organ involvement (e.g. renal, pulmonary or neurologic). IV pulse therapy can be used, or
 - Corticosteroids plus rituximab.
- **Maintenance therapy:** Corticosteroid-sparing agents (Methotrexate, azathioprine, mycophenolate mofetil and IVIg).

Other disorders associated with antineutrophil cytoplasmic antibodies (ANCA) HL

- **Inflammatory bowel disease:** Ulcerative colitis & Crohn's disease.
- **Autoimmune liver disease:** Autoimmune hepatitis, primary sclerosing cholangitis, primary biliary cirrhosis.
- **Autoimmune connective tissue disease:** Systemic LE, rheumatoid arthritis, systemic sclerosis, Sjogren's syndrome, dermatomyositis, reactive arthritis, relapsing polychondritis, antiphospholipid syndrome.
- **Drug-induced vasculitis/lupus/hepatitis:** Propylthiouracil, minocycline, sulfasalazine, TNF- α inhibitors, high-dose intravenous immunoglobulin.
- **Other cutaneous &/or systemic vasculitides:** Mixed cryoglobulinemia, Behçet's disease, Henoch-Schönlein purpura.
- **Infections:** Respiratory tract infections (bacterial/mycobacterial/fungal), HIV, parvovirus B19, malaria, leprosy Hepatitis C virus infection, subacute bacterial endocarditis.
- **Cystic fibrosis (80%).**
- **Hypergammaglobulinemia.**

Localized forms of cutaneous vasculitis ¹

Both show cutaneous vasculitis with variable leucocytoclasia & absence of systemic involvement in spite of a prolonged course.

I) Erythema elevatum diutinum "EED"

It is a rare condition, consisting of persistent brown-red or purple papules, nodules and plaques located in symmetrical distribution on the extensor surface of extremities, elbows, knees and on the dorsa of hands and feet. The lesions at first are soft, but become hard latter due to fibrosis. Healing occurs without scarring leaving hyperpigmentation. Perilesional bullae and vesicles may occur.

Histopathology: Dense perivascular infiltrate, predominantly neutrophilic. Some of neutrophils show leucocytoclasia. There is swelling of endothelial cells and deposits of fibrinoid material within and around the vessel walls. Later on there is granulation tissue and perivascular, concentric or storiform fibrosis with mixed inflammation that is composed predominantly of neutrophils.

Intracellular lipidosis, previously termed "extracellular cholesterosis", is a classic finding in late-stage lesions. It is characterized by 2ry extracellular lipid deposits (cholesterol esters).

DIF: Perivascular deposits of IgG, IgA, IgM, C' and fibrin. It is a leukocytoclastic vasculitis with an immune complex etiology.

Histogenesis

- Reaction to streptococcal intradermal Ag.
- Several cases are associated with HIV infection.
- E. coli may play a role.
- Abnormal serum protein IgA, IgD.

There is association of EED and monoclonal gammopathy. Although IgA gammopathy is most common, IgG has been reported. It usually precedes the onset of paraproteinemia, so immunoelectrophoresis or immunofixation should be part of laboratory evaluation of EED.

Treatment

- Dapsone is the treatment of choice.
- Intralesional corticosteroids may be helpful for mild cases, but systemic corticosteroids are rarely indicated.

Causes of Grenz zone

- Granuloma faciale.
- Lepromatous leprosy.
- Lymphocytoma.

II) Granuloma faciale

There is persistent single or multiple, soft, brownish red, slowly enlarging nodules or plaques always limited to the face. The follicular openings are dilated may be with telangiectasia.

Eosinophilic angiocentric fibrosis: A sinonasal mucosal variant and rarely there is involvement of other sites in the upper respiratory tract.

Histopathology: Dense polymorphous infiltrate is found in the dermis, separated from the epidermis and pilosebaceous appendages by a narrow zone of normal collagen "**Grenz zone**". The infiltrate consists of eosinophils and neutrophils often showing leucocytoclasia. The capillaries are dilated and show eosinophilic fibrinoid material within and around the walls.

DIF: Extensive granular or band-like deposits of IgG, C or IgM & IgA along the basement membrane zone in & around the walls of vessels. It is regarded as a chronic form of leukocytoclastic vasculitis.

Treatment

- **1st line:** Intralesional triamcinolone (2.5-5 mg/ml).
- **Physical modalities:** Surgical excision, cryosurgery, dermabrasion, electrosurgery and CO₂ or pulsed dye laser therapy.
- **For recalcitrant cases:** Oral dapsone (50-150 mg daily), oral clofazimine (300 mg daily), topical PUVA and topical calcineurin inhibitors (pimecrolimus, tacrolimus).

Cryoglobulinemia^①

Cryoglobulins are immunoglobulins that precipitate on cooling (at 4°C) and redissolve on warming (to 37°C).

These cryoglobulins may contain single immunoglobulin (IgG, IgA or IgM) or a mixture of immunoglobulins (IgG-IgM or IgM-IgA). Large amounts of cryoglobulins are seen in patients with multiple myeloma or macroglobulinemia and lesser amounts (<25 mg/100 ml) in other disorders.

Etiology

• Essential "Idiopathic".

• Secondary:

- **Autoimmune diseases:** SLE, Sjögren's syndrome, rheumatoid arthritis, polyarteritis nodosa, polymyositis.
- **Infection:** Hepatitis C, B & A, syphilis, leprosy, subacute bacterial endocarditis.
- **Neoplastic:** Multiple myeloma, lymphoma, Hodgkin's disease, dysproteinemia.
- **Others:** Macroglobulinemia, liver cirrhosis, sarcoidosis.

About 80% of cases of types II and III are secondary to HCV infection.

Classification of cryoglobulins

Subtype	Molecular composition	Associations	Pathophysiology	Clinical manifestations
I	Monoclonal IgM > IgG†	Plasma cell dyscrasias, lymphoproliferative disorders	Vascular occlusion	Raynaud's phenomenon, retiform purpura, gangrene, acrocyanosis
II*	Monoclonal IgM† (>IgG†) against polyclonal IgG	HCV, HIV, autoimmune connective tissue diseases, lymphoproliferative disorders	Vasculitis	Palpable purpura, arthralgias, peripheral neuropathy, glomerulonephritis
III*	Polyclonal IgM† against polyclonal IgG			

* Referred to as "mixed" cryoglobulins because either monoclonal or polyclonal immunoglobulins bind to polyclonal immunoglobulins.

† Typically have rheumatoid factor activity (i.e. are directed against the Fc portion of IgG).

‡ Rarely IgA.

Clinical presentations of cryoglobulinemia

- Majority of patients:
 - **Vasculitic lesions of the skin** (Figs 39-42): Erythematous or purpuric macules or papules, infarction, hemorrhagic crusts and ulcers especially over legs.



Fig. 39. Cryoglobulinemic vasculitis



Fig. 40. Cryoglobulinemic vasculitis

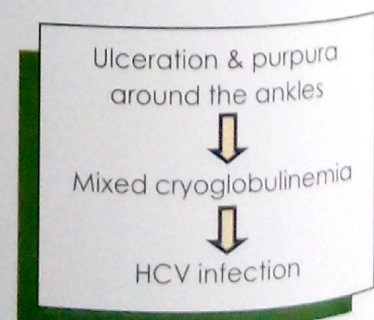


Fig. 41. Cryoglobulinemic vasculitis



Fig. 42. Cryoglobulinemic vasculitis

- **Arthralgia** (70%): Of both small and large joints, rarely arthritis.
- **Fatigue.**
- **Commonly:**
 - **Liver involvement:** Hepatomegaly, chronic active hepatitis, chronic persistent hepatitis or cirrhosis.
 - **Renal involvement:** Isolated proteinuria, hematuria, nephrotic syndrome, nephritic syndrome or acute renal failure.
 - **Raynaud's phenomenon.**
 - **Pulmonary involvement:** Dyspnea, cough or pleurisy.



- In a minority of patients:

- **Neurologic vasculitic involvement** with subsequent peripheral neuropathy.
- **Gastrointestinal vasculitic involvement** with severe abdominal pain.
- **Lymphadenopathy.**
- **Sjögren's syndrome.**
- **Splenomegaly.**

Pathogenesis of disease in cryoglobulinemia

- Cause of precipitation in cold: Unknown.
- Cause of autoantibody formation as cryoglobulins, probably due to:
 - Defective monocyte-macrophage function.
 - Defective leukocyte function.
- Mechanisms for the development of associated diseases:
 - Aggregation/precipitation within vascular lumen.
 - Immune complex-mediated changes secondary to slow subendothelial deposition of complexes.

Investigations

- Cryocrit: Estimation of the packed volume of precipitate after centrifugation of pre-cooled serum ± gel electrophoresis.
- ↑ ESR.
- +ve rheumatoid factor.
- ↑ Ig level.
- Skin biopsy.
- **Tests for cryoglobulins:**
 - Assayed during clinical flares.
 - On more than one occasion.
 - The blood sample should be kept at 37°C while being transported to the laboratory.

Management

- Treatment of underlying disease(s), e.g. Interferon-α plus ribavirin for patients with HCV-associated mixed cryoglobulinemia.
- In essential types:
 - NSAIDs and physical measures (bed rest and avoid cold) for mild cases.
 - Severe cases:
 - Corticosteroid, 15-80 mg/day.
 - ± Immunosuppressives: Chlorambucil, azathioprine.
 - ± Antimalarials.
 - Plasmapheresis.
 - Rituximab.

Markers for evaluating effectiveness of treatment

- Clinical progress.
- Rheumatoid factor.
- Cryocrit.
- Complement component levels.

Panniculitis



- Panniculitis represents a group of heterogenous inflammatory diseases that involves the subcutaneous fat.
- Etiological classification of panniculitis:
 - Metabolic panniculitis.
 - Physical & chemical panniculitis.
 - Immunologic panniculitis.
 - Connective tissue disease panniculitis.
 - Vascular panniculitis.
 - Miscellaneous panniculitis.
- It presents clinically as subcutaneous erythematous nodules on the lower extremities with or without erythema, ulceration, drainage, warmth and pain or tenderness. Infection may occur.
- Histopathological classification of panniculitis:
 - Septal panniculitis.
 - Lobular panniculitis.
 - Mixed panniculitis.
 - Panniculitis with vasculitis.



Panniculitis

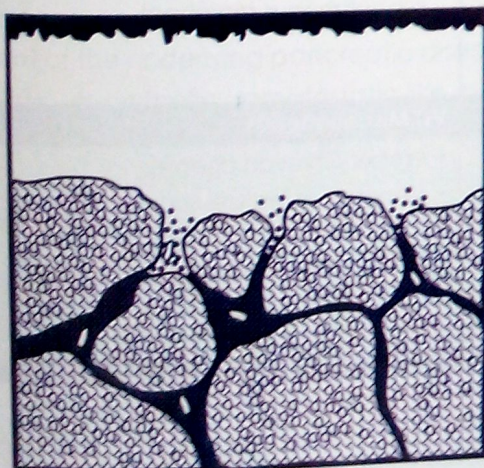
Panniculitis represents a group of heterogeneous inflammatory diseases that involves the subcutaneous fat. It presents clinically as subcutaneous erythematous nodules on the lower extremities with or without erythema, ulceration, drainage, warmth and pain or tenderness. Infection may occur.

Classifications

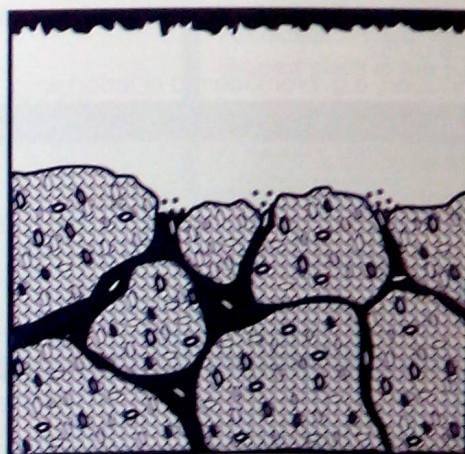
Either etiological or histopathological.

Histopathologically, panniculitis may be:

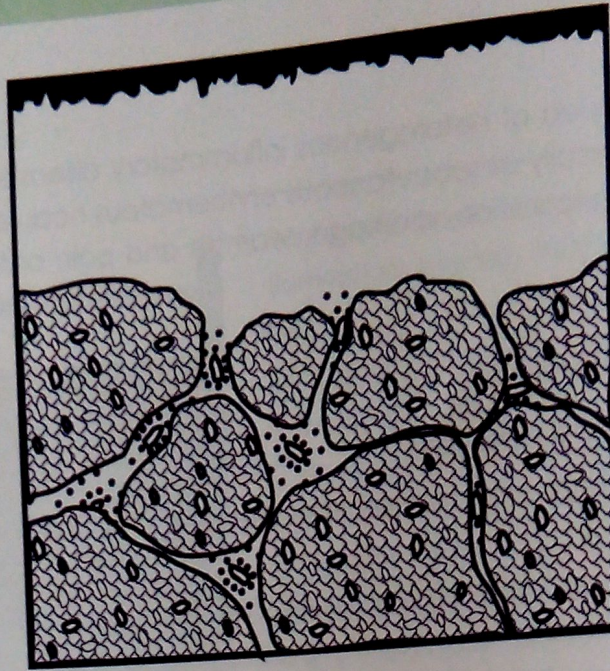
- **Septal panniculitis:** Includes erythema nodosum, erythema nodosum migrans, and eosinophilic panniculitis.
- **Lobular panniculitis:** Includes relapsing febrile nodular panniculitis (Weber-Christian syndrome), idiopathic nodular panniculitis, lipotrophic panniculitis, panniculitis associated with crystal deposition (sclerema neonatorum), subcutaneous fat necrosis of newborn, gout, poststeroid panniculitis and panniculitis due to drugs as pentazocine, enzymic (pancreatic) panniculitis, α 1-antitrypsin deficiency panniculitis, fat necrosis (cold panniculitis, nodular cystic fat necrosis, lipomembranous fat necrosis), lymphomatous panniculitis, and cytophagic histiocytic panniculitis.
- **Mixed panniculitis:** Includes lupus erythematosus profundus, scleroderma (fasciitis with eosinophilia), subcutaneous sarcoidosis, subcutaneous granuloma annulare, necrobiosis lipoidica, infective panniculitis, factitious panniculitis (e.g. sclerosing lipogranuloma, oil granuloma), sclerosing panniculitis (lipodermatosclerosis), and fasciitis-panniculitis syndrome.
- **Panniculitis with vasculitis:** Includes small-vessel vasculitis, large-vessel vasculitis (e.g. polyarteritis nodosa), and neutrophilic panniculitis.



Panniculitis, mostly septal



Panniculitis, mostly lobular



Panniculitis, septal & lobular

Classification of panniculitis (etiological)

I) Metabolic	II) Physical & chemical
• $\alpha 1$-antitrypsin deficiency • Subcutaneous nodular fat necrosis in pancreatic disease. • Newborn fat necrosis: • Sclerema neonatorum. • Subcutaneous fat necrosis of the newborn.	• Cold panniculitis. • Faciitital panniculitis. • Post-steroid panniculitis
III) Immunologic	IV) Connective tissue disease
• Erythema nodosum. • Erythema nodosum migrans. • Erythema induratum (with TB) or nodular vasculitis (in absence of TB). • Drug-induced, e.g. bromoderma or iododerma.	• LE profundus. • Morphea profunda (eosinophilic fasciitis subcutaneous morphea).
V) Vascular	VI) Miscellaneous
• Polyarteritis nodosa. • Superficial migratory thrombophlebitis.	• Weber-Christian disease. • Lipogranulomatosis subcutanea of Rothmann-Makai. • Subcutaneous sarcoidosis (Darrier Roussy). • Subcutaneous granuloma annulare. • Histiocytic cytophagic panniculitis.

Metabolic panniculitis

$\alpha 1$ -antitrypsin deficiency

$\alpha 1$ -antitrypsin is produced in the liver to inhibit proteases which are involved in lymphocytes and phagocytes activation. $\alpha 1$ -antitrypsin deficiency may accelerate lymphocytes and phagocytes activation $\rightarrow$ severe inflammation and tissue necrosis, 2ry to protease action. There is partial or total deficiency of $\alpha 1$ -antitrypsin in different patients.

Clinically: Recurrent tender nodules that undergo spontaneous ulceration or drainage of oily yellow fluid. They occur commonly on the trunk and proximal extremities. The lesions may be precipitated by trauma or surgical debridement which should be avoided.

Histopathology: The subcutis shows mixed infiltrate of round cells and neutrophils intermingled with lipophages. This is followed by widespread necrosis of subcutis → necrotic ulcers.

Treatment

- Dapsone: 150 mg/day
- IV infusion of $\alpha 1$ -proteinase inhibitor concentrate in severe form.

Subcutaneous nodular fat necrosis in pancreatic disease (Pancreatic panniculitis)

This may occur in patients with pancreatitis or pancreatic cancer.

Clinically: Painful red nodules, some of which may be fluctuant but rarely drain an oily substance.

The most common site is the pretibial region and around the ankles and knees, but may occur on thighs and buttocks. It may be associated with arthritis (especially of the ankles) which is of diagnostic importance.

Histopathology (mostly lobular panniculitis): Multiple foci of fat necrosis with "ghost-like" fat cells (thick, shadowy walls and no nuclei) and basophilic Ca deposits. Surrounding the foci of fat necrosis, there is a polymorphous inflammatory infiltrate consisting of neutrophils, lymphocytes, histiocytes, foamy cells and foreign body giant cells.

Pathogenesis: The release of pancreatic enzymes mainly amylase and lipase into the circulation → subcutaneous fat necrosis. Resistance of the fat cell membrane to lipase → "ghost cells". Fatty acids formed by lipolysis combine with Ca → Ca deposits. It represents saponification of fat by calcium salts.

Treatment

- Treatment of the underlying pancreatic disease.
- Octreotide, a synthetic somatostatin-like polypeptide, can be used to inhibit pancreatic enzyme production.

Panniculitides with needle-shaped clefts in the subcutis:

- Sclerema neonatorum.
- Subcutaneous fat necrosis of the newborn.
- Post-steroid panniculitis.

Newborn fat necrosis

A) Sclerema neonatorum

It is a rare disease affecting infants during the first few days of life. There is diffuse hardening of the entire subcutaneous fat. The entire skin has a waxy appearance, feels cold, tight, sclerotic and non-pitting induration. There is difficulty in respiration and in feeding and death occurs within a few days.

Pathogenesis: It is due to increased ratio of saturated to unsaturated fatty acids in subcutaneous triglycerides → crystal formation, fat necrosis and inflammation.

Histopathology: Thickening of subcutaneous tissue due to increase in size of fat cells and the presence of wide, intersecting fibrous bands. Many of fat cells are filled with fine, needle-like clefts. In frozen sections, these clefts are occupied by crystals. Inflammatory infiltrate is sparse or absent.

Treatment

- Treatment of underlying disease.
- Repeated exchange transfusions may reduce mortality.

B) Subcutaneous fat necrosis of the newborn

It is a rare disease affecting infants during the first few days of life. There is fat necrosis in the subcutaneous tissue. Multiple indurated, non-pitting nodules and plaques develop and usually undergo spontaneous resolution mainly in buttocks, thigh and cheeks (Figs 43, 44). Some of the nodules discharge a caseous material. The infant's general health is usually not affected. Hypercalcemia may be associated.

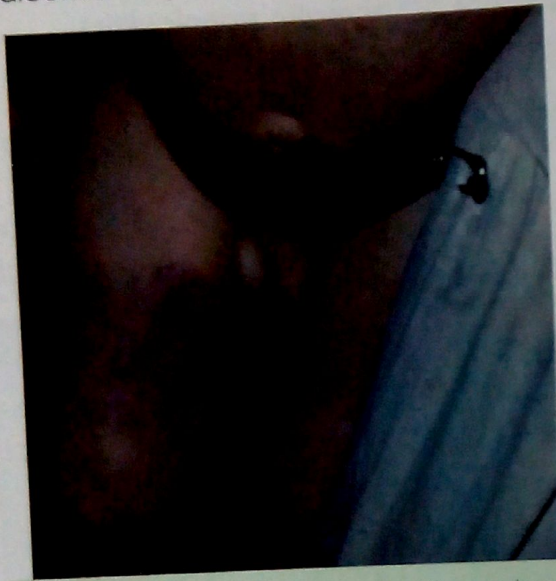


Fig. 43. Subcutaneous fat necrosis of the newborn



Fig. 44. Subcutaneous fat necrosis of the newborn

Histopathology (mostly lobular panniculitis): Foci of fat necrosis in the subcutaneous tissue infiltrated by lymphocytes, histiocytes and foreign body giant cells. Many of the fat cells contain needle-shaped clefts which lie in a radial fashion. Ca deposits are scattered.

Treatment

Hypercalcemia is managed by:

- Hydration, dietary restriction of both calcium and vitamin D, calcium-wasting diuretics (e.g. furosemide), calcitonin and bisphosphonates (e.g. etidronate, pamidronate), corticosteroids.

	Sclerema neonatorum	Subcutaneous fat necrosis
General health of the infant	Severely ill.	Healthy.
Sites	Generalized.	Trunk, buttocks, thighs.
Clinically	Diffuse waxy appearance of the entire skin.	Multiple indurated nodules & plaques.
Histology	Lack of inflammatory infiltrate.	Dense inflammatory infiltrate of histiocytes and lymphocytes.
Prognosis	Poor.	Excellent.

Physical & chemical panniculitis

Traumatic panniculitis

Numerous forms of trauma, either accidental or purposeful can produce painful subcutaneous nodules or plaques.

Cold panniculitis

Infants are more susceptible to cold panniculitis as the fatty acids of the subcutaneous tissue are more highly saturated in the newborn than in the adult. Therefore, their fat solidifies more easily at a lower temperature.

There are ill-defined, red, indurated plaques or nodules which develop on exposed areas as face few hours after exposure to severe cold. They subside spontaneously within 2 weeks without scarring. "Popsicle" panniculitis of the angle of the mouth and the cheeks has been described in children who frequently suck ice-lollies.

Histopathology (mostly lobular panniculitis): Lymphocytic inflammation is seen scattered in the fat lobules. Epidermis and dermis are normal.

DD: Pernio is limited to the acral portion of extremities and affects mainly the dermis.

Factitial panniculitis

It results from surreptitious injections of substances into the subcutaneous tissue, e.g. morphine, pentazocine or meperidine by drug addicts or milk or stool by mentally disturbed patients.

Also, injection of oily substances as paraffin, mineral oil, or silicon may produce a similar picture. It is regarded as a foreign body reaction.

Clinically: There is a bizarre clinical picture depending on the substance and site injected. There may be discharging nodules, ulcers or scars.

Histopathology: Mostly lobular panniculitis with inflammatory infiltrate mainly of neutrophils with absence of vessel involvement. Injection of oily materials or silicone → Paraffinoma: Oily cysts surrounded by fibrosis and inflammation (Swiss-cheese appearance).

Poststeroid panniculitis

• **Onset:** 1-40 days after cessation of high-dose systemic corticosteroid therapy (Follows rapid corticosteroid withdrawal).

• **Clinical picture:** Firm red plaques on cheeks, arms, trunk; small and discrete or large and confluent lesions; pruritic, tender or asymptomatic.

• **Histopathology:** Lobular panniculitis with lymphocytes, macrophages, multinucleated giant cells; needle-shaped clefts in lipocytes and giant cells.

• Spontaneous remission without scarring usually occurs after several weeks.

Malignancy such as poorly differentiated carcinoma, lymphomas, multiple myeloma and leukemias may produce subacute nodules that mimic other forms of panniculitis. The diagnosis depends on the presence of cytologic atypia, "lining-up" of atypical cells between the collagen bundles and minimal alteration of CT in the face of dense cellular infiltration.

Immunologic panniculitis

Erythema nodosum²

It is the most common type of panniculitis (mostly septal, without vasculitis) characterized by erythematous nodules, typically over the pretibial areas. It is an acute inflammatory/immunologic reaction pattern of the subcutaneous tissue caused by multiple etiologies.

Age: 20-40 years.

Sex: More in females (3:1).

Pathogenesis: Erythema nodosum is considered a reactive erythema due to many etiological factors. It may be due to formation of immune complexes and their deposition in and around vessels in deep dermis and adipose tissue (septal panniculitis), however, DIF very rarely showing immunoglobulins deposition in the vessel walls.

Clinical manifestations (Figs 45-48): There are multiple, bilateral and symmetric, tender, warm, red nodules located mainly on the anterior aspects of the lower legs, although they may occur on the thighs and forearms. The lesions are frequently accompanied by fever, malaise, arthralgias and leukocytosis.

The lesions run an acute course characterized in regression by bruise-like color changes that may persist for months. Spontaneous healing occurs in 3-6 weeks without ulceration or scarring. Recurrences are frequent.



Fig. 45. Erythema nodosum

Etiology of erythema nodosum

- **Infections:**
 - **Bacterial:**
 - Streptococcal*, e.g. sore throat due to β -hemolytic streptococci.
 - TB, especially in children.
 - Yersinia, salmonellosis.
 - **Viral:** Milker's nodes, infectious mononucleosis, hepatitis B.
 - **Chlamydia:** Lymph. Venereum, cat-scratch disease, psittaci.
 - **Mycoses:** Kerion, coccidioidomycosis & blastomycosis, histoplasmosis.
- **Drugs*:** Contraceptive pills, sulphonamides, blastomycosis, histoplasmosis.
- **Malignancy:** Leukemia, Hodgkin's disease.
- **Miscellaneous:** Sarcoidosis*, Löfgren's syndrome, ulcerative colitis, Behçet's disease.
- **Idiopathic (30%):** No apparent cause.

* The most common cause.

Streptococcal infections, drugs, sarcoidosis & ulcerative colitis are the most common etiological factors in EN.



Fig. 46. Erythema nodosum



Fig. 47. Erythema nodosum



Fig. 48. Erythema nodosum

Histopathology (Figs 49-51): Deep skin biopsy that includes subcutaneous tissue in the center of the lesion is a must. Punch biopsies are inadequate. **It is mostly septal panniculitis without vasculitis:** A septal inflammatory infiltrate associated with septal vascular endothelial swelling, edema and hemorrhage. The infiltrate extends from the septal tissue into fat lobule in a lace-like fashion. Later, there is predominance of lymphocytes and histiocytes together with giant cells. There is no leukocytoclastic vasculitis or fat necrosis.

The presence of Miescher's radial granulomas is characteristic consisting of small, well-defined nodular aggregations of small histiocytes around a central stellate or banana-shaped cleft. They are present in the septa.

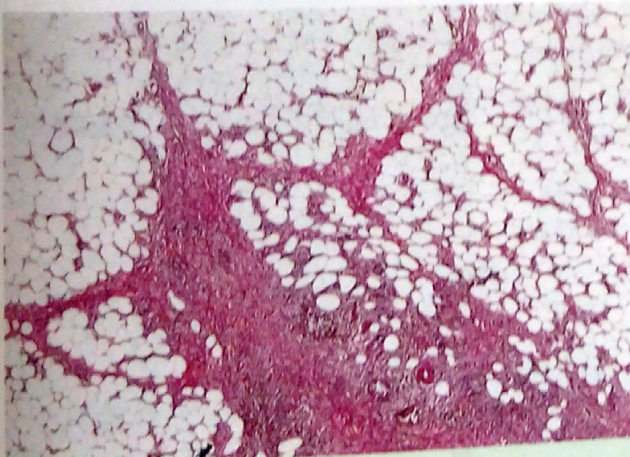


Fig. 49. Histopathology of erythema nodosum

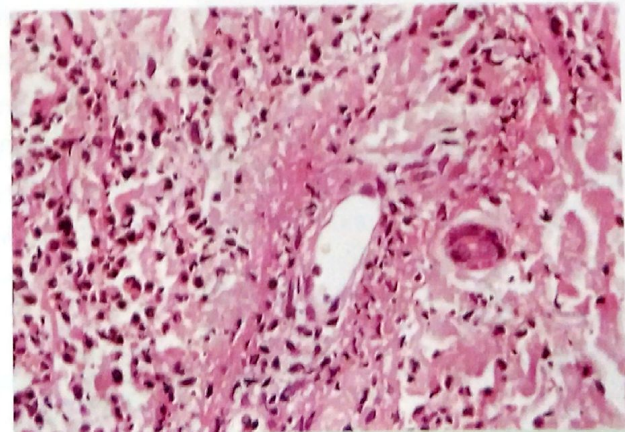


Fig. 50. Histopathology of erythema nodosum

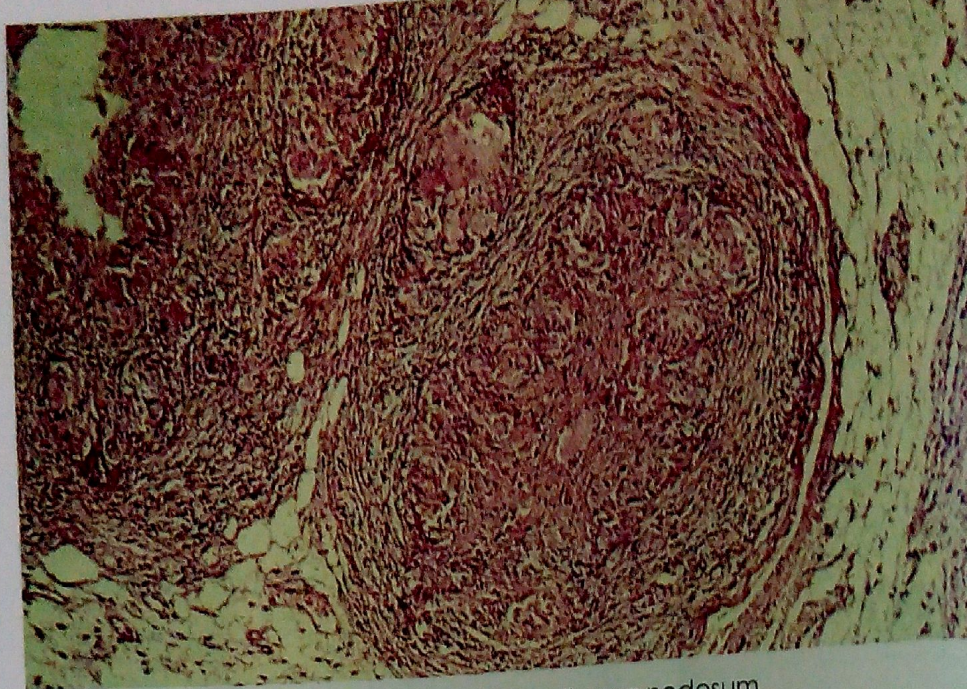


Fig. 51. Histopathology of erythema nodosum

Laboratory findings

- Elevated SR, mild anemia, leukocytosis.
- Chest X-ray: Hilar adenopathy or infiltrates (sarcoid Lofgren syndrome).
- ASO-titer raised & throat swab & culture (streptococcal).
- Intradermal skin tests (TB, sarcoidosis, deep mycoses).

DD

- Erythema induratum of Bazin (nodular vasculitis) appears more in the calves, liable to ulceration & scar formation.
- Erythema nodosum leprosum: Occurs in lepromatous leprosy with leukocytoclastic vasculitis in histopathology.
- Polyarteritis nodosa: Small purpuric nodules that may ulcerate together with a livedoid pattern. There is leukocytoclastic vasculitis.

Treatment

- Treatment of the underlying cause.
- Complete bed rest.
- NSAID drugs, e.g. Acetyl salicylic acid or indomethacin.
- Potassium iodide 900 mg/day or as saturated solution 2-10 drops in orange juice 3 times daily (adult dosages range from 300 to 1500 mg/day) for 3-4 weeks (Lobestra syp®). It leads to heparin release from mast cells → -DHR and it inhibits neutrophil chemotaxis.

NB: Systemic steroids are not indicated.

Findings suggestive of a systemic cause for erythema nodosum

- Synovitis.
- Diarrhea.
- Abnormal chest X-ray.
- Preceding upper respiratory tract infection.
- Elevated antistreptolysin O &/or anti-DNase B titers.
- Positive tuberculin skin test.

Dermatoses on the shin of tibia

Itchy

- Lichen simplex chronicus.
- Hypertrophic lichen planus.
- Lichen amyloidosis.
- Prurigo nodularis.

Non-itchy

- Erythema nodosum.
- NBLD.
- Ecthyma.
- Pretibial myxedema.

Erythema nodosum migrans "Subacute nodular migratory panniculitis"

One or few red subcutaneous nodules are found more unilaterally on the lower legs, more on the lateral rather than the anterior side. The lesions are more tender and more persistent (for 4-5 months) than those of erythema nodosum. Bruising does not occur. Through peripheral extension (crescentic shape).

Nodular vasculitis²

Synonym

- Erythema induratum of Bazin or Bazin's disease (tuberculous etiology).
- Erythema induratum of Whitfield (non-tuberculous etiology).

It is a form of lobular panniculitis associated with subcutaneous vasculitis.

Age: Middle-aged.

Sex: Usually females.

Clinically (Figs 52, 53)

Erythematous, tender or asymptomatic subcutaneous nodules or plaques on the posterior aspects of lower legs, rarely on shins, thighs and buttocks. Ulceration and drainage sometimes occur. They persist for prolonged periods before healing with atrophic scars. There may be associated ischemic changes, e.g. cool and edematous skin. Venous insufficiency and varicose veins may occur. Recurrent episodes are common.



Fig. 52. Nodular vasculitis



Fig. 53. Nodular vasculitis

Pathogenesis

It is considered to be an immune complex vasculitis that is triggered by a variety of antigenic stimuli. Mycobacterial DNA has been identified using polymerase chain reaction in some cases (Erythema induratum of Bazin).

Histopathology (Figs 54-57)

It is mostly lobular panniculitis with a mixed infiltrate that may be granulomatous. Medium-sized vessel vasculitis is often present leading to ischemic necrosis of fat lobule → granulomatous in-

inflammation consists of lymphocytes, histiocytes, epithelioid cells and giant cells. Caseous necrosis is present in 50% of cases and even in cases not associated with TB.

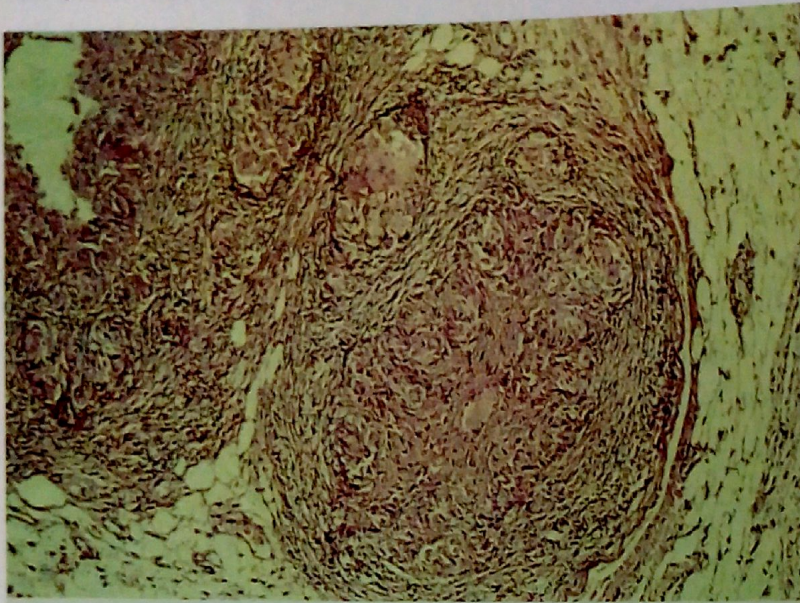


Fig. 54. Histopathology of nodular vasculitis

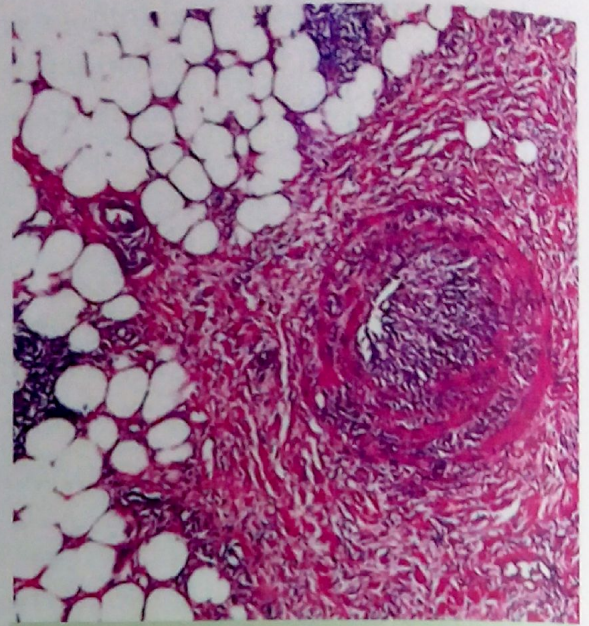


Fig. 55. Histopathology of nodular vasculitis

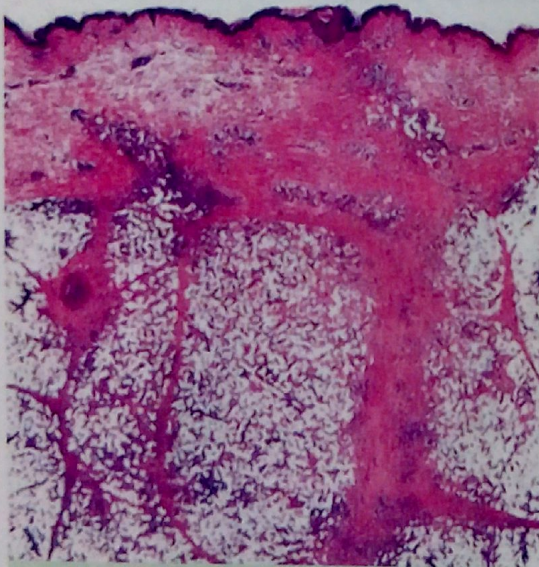


Fig. 56. Histopathology of nodular vasculitis

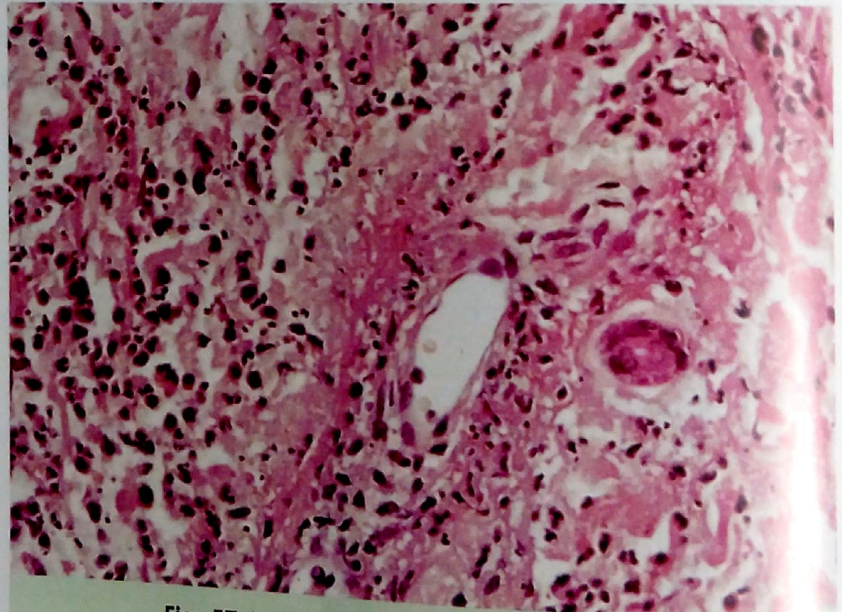


Fig. 57. Histopathology of nodular vasculitis

Treatment

- Antituberculous therapy, for cases associated with TB.
- Bed rest, tetracyclines, NAIDs and potassium iodide.
- Systemic steroids may be effective.
- Dapsone.

Vascular panniculitis

polyarteritis nodosa "Periarteritis nodosa" ①

Segmental vasculitis of predominantly medium-sized arteries.

There are 2 types:

1. **Systemic (classic) periarteritis nodosa (SPAN):** Cutaneous (in 25% of cases) and systemic manifestations.
2. **Cutaneous periarteritis nodosa (CPAN):** Cutaneous lesions predominate.

Systemic periarteritis nodosa "SPAN"

There is severe necrotizing vasculitis of small and medium-sized arteries of many internal organs.

Clinical manifestations: It follows an intermittent course which may be fatal within months or years.

- **Cutaneous lesions** (10-15% of cases): Usually limited to the lower extremities and consist of: painful erythematous subcutaneous nodules appearing in crops, livedo reticularis, retiform purpura, punched-out ulcers, ecchymoses and gangrene.
- **Systemic manifestations:** The kidney is the most frequently involved organ. Renal insufficiency is the most common cause of death. Other manifestations include: Fever, weakness, myalgia, arthralgia, hypertension, GIT manifestations (abdominal pain, bleeding), cardiac insufficiency, CNS affection, polyneuritis & ocular affection. The lung is usually spared. Renal biopsy is essential for diagnosis.

Juvenile polyarteritis nodosa with coronary arteritis may be an example of Kawasaki disease.

Cutaneous periarteritis nodosa "CPAN" (Livedo with nodules)

It is characterized by necrotizing vasculitis of the skin sparing visceral arteries. It follows a chronic, relapsing benign course.

Clinical manifestations

- Painful nodules usually on the lower extremities, livedo reticularis and ulceration.
- Systemic manifestations include fever, arthralgia, myalgia and peripheral neuropathy.

Histopathology

There is segmental necrotizing vasculitis of medium-sized and small arteries of the septa of the upper subcutis. There is degeneration of arterial wall with deposition of fibrinoid material. Focal areas of involvement result in vessel wall weakening and necrosis, leading to aneurysmal dilation and/or stenosis. Neutrophilic infiltrates with evidence of leukocytoclasia are present within and around the arterial wall. Later on, intimal proliferation, thrombotic occlusion of lumen and ulceration occur.

The ACR classification criteria for polyarteritis nodosa (PAN) HL

- Weight loss >4 kg.
- Livedo reticularis.
- Testicular pain or tenderness.
- Myalgias, myopathy or tenderness.
- Neuropathy.
- Hypertension (diastolic BP >90 mmHg).
- Renal impairment (elevated BUN or creatinine).
- Hepatitis B virus.
- Abnormal arteriography.
- Biopsy of artery showing PMN.

Three criteria classify PAN with sensitivity of 82.2% & specificity of 86.6%.

DIF: Deposits of C3, IgM and fibrin within or around vessel walls.

Pathogenesis

- SPAN may be associated with collagen-vascular disorders, e.g. SLE, RA, with hepatitis B virus infection or HIV infection. The condition is immune-complex mediated.
- In contrast to SPAN, ANAs, antineutrophil cytoplasm antibody and rheumatoid factor are lacking in patients with CPAN.

Microscopic polyarteritis nodosa is a term used for segmental necrotizing and crescentic glomerulonephritis in which 30-50% of patients had associated vasculitis of the skin. The presence of P-ANCA and response to prednisolone and cyclophosphamide suggest that it should differ from benign skin conditions.

Polyarteritis nodosa in childhood and infancy: Rare with high incidence of convulsions and lymphadenopathy. Renal and musculoskeletal involvement are usually present. Streptococcal and staphylococcal superantigen may play a role.

Treatment

• Systemic PAN:

- Systemic corticosteroids (e.g. 1 mg/kg/day of prednisone) with the dose tapered over 6 months.
- Refractory cases: Add cyclophosphamide for up to 12 months.
- Therapeutic alternatives: Plasmapheresis and IVIg.
- Treatment of HBV: Interferon-2 α and lamivudine.

• Cutaneous PAN

- Topical or intralesional corticosteroids for localized areas, but progressive or extensive disease may warrant systemic corticosteroids.
- Therapeutic alternatives:
 - NSAIDs.
 - Digital necrosis improves with intravenous prostaglandins or calcium channel blockers.

Superficial migratory thrombophlebitis

It starts as multiple, tender, erythematous nodules most often on the legs but may occur on the arms or abdomen. After several days, a cord-like induration can be felt. Recurrent lesions are usually noted. It may be associated with visceral carcinoma commonly in the pancreas and lung (Trousseau's syndrome), Behçet's disease or Hodgkin's disease.

Histopathology: Inflammatory infiltrates permeate all layers of the wall of a large vein, at the DEJ and thrombosis usually occludes the lumen.

Treatment

- Treatment of the underlying disease.
- Anticoagulant as warfarin or heparin.

Infection-induced panniculitis HL

A wide variety of infectious agents has been reported to produce panniculitis.

Reported causative agents

Bacteria	
• Staphylococcus aureus • Group A streptococcus • Pseudomonas aeruginosa • Nocardia asteroides	
Mycobacteria	
• M. tuberculosis • M. marinum • M. avium-intracellulare • M. chelonae • M. fortuitum • M. ulcerans	
Coxiella	
• C. burnetii	
Borrelia	
• B. burgdorferi	
Fungi	
• Blastomyces • Dermatitidis • Histoplasma capsulatum • Microsporium spp. (including M. canis) • Candida spp. (including C. albicans) • Cryptococcus neoformans • Fusarium spp. • Aspergillus spp. (including A. flavus) • Aureobasidium pullulans	
Helminths	
• Nematodes (Gnathostoma spp.) • Trematodes (Fasciola hepatica)	

Adapted from: Bologna et al., *Dermatology Textbook*, Third edition, 2012.

Lipodermatosclerosis or "sclerosing panniculitis"

- Usually develops in the setting of chronic venous insufficiency, and fibrinolytic abnormalities are also present in these individuals.
- **Clinical picture:**
 - Favors the medial aspect of the lower extremities above the malleolus.
 - **Acute phase:** Erythema, warmth and tenderness, which may be misdiagnosed as infectious cellulitis.
 - **Chronic phase:** Induration (marked sclerosis of the dermis and subcutis) and red-brown to violet-brown discoloration (due to hemosiderin deposition).
- **Histopathology:**
 - Both septal and lobular panniculitis.
 - Lymphocytic infiltrate in the septa that rims the fat lobules, variable degrees of capillary congestion and thrombosis, and hemorrhage with hemosiderin deposition.
 - Advanced lesions show marked septal sclerosis and lipomembranous change.
 - Lipomembranous change: Thickened, undulating membranes "resulting from degenerated cell membranes of lipocytes and/or macrophages" that form cysts and papillary configurations. The material comprising the membranes is ceroid, an oxidation product of unsaturated fatty acids.

• **Treatment:**

- Leg elevation and consistent compression therapy are the mainstays
- Anti-inflammatory: Intralesional corticosteroids.
- Anabolic steroid: Danazol enhances fibrinolysis, and reduces pain, extent of involvement, and induration of the skin. Oxandrolone, an anabolic steroid with less hepatotoxicity and fewer androgenic effects.

HL

Connective tissue panniculitis

Disorder	Clinical presentation	Lesion distribution	Relation to systemic disease	Histopathology of panniculitis
Morphea & scleroderma	Indurated plaques.	Extremities, trunk.	Occurs in scleroderma, but usually more pronounced in morphea.	Septal, with thickening & sometimes mucin deposition; inflammation especially at dermal-subcutaneous interface; lymphocytes & plasma cells; lymphoid follicles in morphea*.
Lupus panniculitis	Tender subcutaneous nodules & plaques; may have overlying lesions of discoid LE.	Face (especially cheeks), upper arms, shoulders, hips, breasts, trunk.	Only minority of cases associated with systemic LE.	Lobular or mixed lobular/septal; mucin deposition; hyaline necrosis of lobules; lymphocytes & plasma cells, sometimes with prominent nuclear dust; nodular lymphocytic aggregates or lymphoid follicles.
Dermatomyositis	Indurated painful plaques & nodules; may ulcerate.	Buttocks, abdomen, thighs, arms.	Can arise in patients with established dermatomyositis or precede other disease manifestations.	Lobular or mixed septal/lobular; fat necrosis, lipomembranous changes; sometimes calcification; lymphocytes & plasma cells; sometimes nodular lymphocytic aggregates.
Annular atrophic connective tissue panniculitis of the ankles	Subcutaneous atrophy, which may be preceded by induration & tenderness.	Circumferential bands around the ankles.	Patients often have antinuclear antibodies &/or autoimmune conditions such as thyroiditis or rheumatoid arthritis.	Lobular or mixed septal/lobular lymphohistiocytic panniculitis with areas of fat necrosis.
Atrophic connective tissue panniculitis	Erythematous, indurated plaques that resolve with subcutaneous atrophy.	Favors extremities; may be widespread.		

* Less often than in lupus panniculitis.

Miscellaneous panniculitis

Weber-Christian disease "Relapsing Febrile Nodular Non-suppurative Panniculitis"

There is episodes of erythematous, tender, subcutaneous nodules, located mainly on the lower legs but may occur on the arms or trunk associated with mild fever. Spontaneous remission occurs leaving depressed areas with residual hyperpigmentation. Rarely, visceral affection may occur. The condition usually affects middle-aged women.

Histopathology: 3 stages are described.

- **First stage:** An acute inflammatory infiltrate composed predominantly of neutrophils is seen between the fat cells.
- **The second stage:** Foam cells (macrophages) invading and digesting the fat cells.
- **The third stage:** Replacement of the foam cells by fibrotic connective tissue.

Pathogenesis: High levels of circulating immune complexes have been reported, which may be responsible for damaging the subcutaneous fat.

Treatment: Systemic steroids, NSAIDs, cyclosporine or cyclophosphamide have been tried.

Panniculitis of Rothman-Makai "Lipogranulomatosis subcutanea"

This form of panniculitis is quite vague in the literature. Some of the reported cases can be regarded as minor variants of Weber-Christian disease, erythema nodosum, or erythema induratum. Such cases are better termed "non-specific panniculitis" or "non-febrile variant of Weber-Christian disease".

Histiocytic cytophagic panniculitis

There is recurrent, widely distributed tender nodules associated with fever, hepatosplenomegaly, pancytopenia and progressive liver dysfunction. Death usually occurs from abrupt hemorrhage.

Histopathology: Lobular panniculitis infiltrated with massive histiocytic and multiple "bean-bag" cells (giant histiocytes engulfing erythrocytes, lymphocytes and/or karyorrhectic debris).

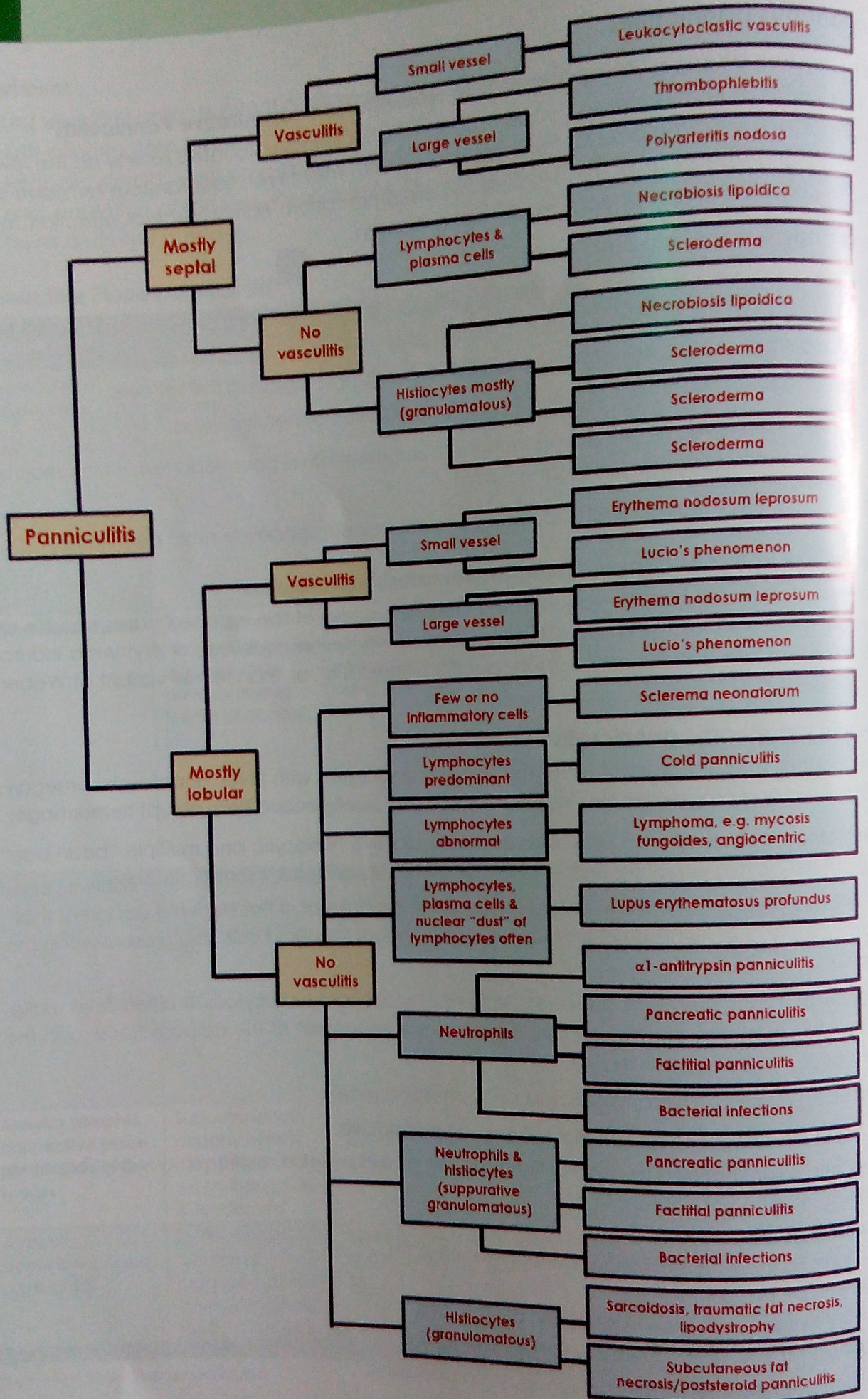
With the advent of immunophenotyping and genetic techniques, it has become apparent that the vast majority of patients have lymphoma, with atypical lymphoid cells also present within the panniculus.

Pathogenesis: It may represent a low-grade form of malignant histiocytosis. It differs from malignant histiocytosis by the chronic course, the primary involvement of the adipose tissue, and the benign histiocytes in the infiltrate.

Treatment: Prednisone, chlorambucil and cyclophosphamide.

The approach to diagnose an "Unknown" case of panniculitis

- **History and examination:** Location of the eruption and its onset in relation to any possible drug ingestion, infection or trauma.
- **Laboratory studies:**
 - Culture: For possible streptococcal pharyngitis in EN.
 - ANAs: For lupus panniculitis.
 - α 1-antitrypsin level: For α 1-antitrypsin panniculitis.
- **Skin biopsy:** Mostly septal or mostly lobular with or without vasculitis.
- **Immunohistochemistry:** Where malignancy is a possibility.



Lipodystrophy

This is an abnormality of fat, atrophy (lipoatrophy, more common), or hypertrophy (less common), and often associated with insulin-resistant DM.

Classified according to its extent into:

A) Localized

Insulin lipodystrophies:

- At the injection site in 40% of insulin-dependent diabetics.
- Atrophy or hypertrophy (more common).
- Usually seen in women and children, rarely in men.
- It may be due to antibodies to insulin.
- Spontaneous recovery occurs when the site of injection is changed.
- Prevention is by constant alteration of the site of injection.

Idiopathic lipoatrophy:

	Lipoatrophia semi-circularis	Centrifugal lipodystrophy
Clinical picture	Circular depression 2-4 cm in diameter.	Central large bluish depressed area with a centrifugal spread.
Site	Thighs.	Abdomen.
Age	Adults.	Children.

B) Partial

Partial lipoatrophy:

- Face: Symmetrical disappearance of fat → cadaveric appearance.
- Upper half of the body: Complete loss of SC fat.
- Lower part of the body: Hypertrophy of the SC fat (some cases).
- Hemilipodystrophy, involving half of the face or body occurs in 10%.
- Association: Glomerulonephritis 90%, insulin-dependent diabetes in 30%.

Partial face-sparing lipodystrophy:

- Widespread but partial absence of subcutaneous fat, sparing the face.

Lipodystrophy associated with protease inhibitors:

- Protease inhibitors → peripheral lipoatrophy and central adiposity.
- Withdrawal of these drugs does not improve the lipodystrophy.

C) Generalized

- May be congenital as Berardinelli-Seip syndrome (AR- total loss of SC and visceral fat) and may be acquired (the patients have acromegaloid features and enlargement of the skin of hands and feet).
- Excessive appetite and accelerated growth.
- Hyperlipaemia, diabetes.

Neutrophilic Dermatoses



- The neutrophilic dermatoses constitute a heterogeneous but linked spectrum of diseases, with significant overlapping histopathologic findings & similar pathogenic mechanisms & therapeutic approaches.
- The cutaneous manifestations vary from vesiculopustules & plaques to nodules and ulcers. It is noteworthy that there may be several different types of lesions in the same patient.
- The dermatosis may be localized or more widespread, and, in an occasional patient, similar sterile neutrophilic infiltrates may occur in the eyes, joints, bones, lung, liver and lymph nodes. Internal diseases may have significant morbidity and mortality.
- Histologically, these disorders are characterized by perivascular and diffuse neutrophilic infiltrates without any identifiable infectious agents. The neutrophilic infiltrate may be most prominent in the epidermis, dermis or even the panniculus.

Sweet's syndrome

- Constitutional signs and symptoms such as fever and malaise.
- Clinically, erythematous plaques that are occasionally painful.
- Histologically, dense perivascular neutrophilic infiltrate, edema & infrequently, bullae; leukocytoclasia with minimal to no evidence of vasculitis.
- Associated conditions include infections, malignancies (especially acute myelogenous leukemia), inflammatory bowel disease, autoimmune disorders, drugs and pregnancy.

Pyoderma gangrenosum

- Four major clinical forms: Ulcerative, bullous, pustular and superficial granulomatous.
- Initial lesion is often a pustule on an erythematous or violaceous base, an erythematous nodule, or a bulla.
- Characteristic lesion is an ulcer with a necrotic undermined border; the base may be purulent or vegetative.
- Histologically, a sterile dermal or adnexal abscess (without a vasculopathy) is seen in active, untreated, expanding lesions.
- Associated illnesses include inflammatory bowel disease, arthritis, monoclonal gammopathies and other hematologic disorders.

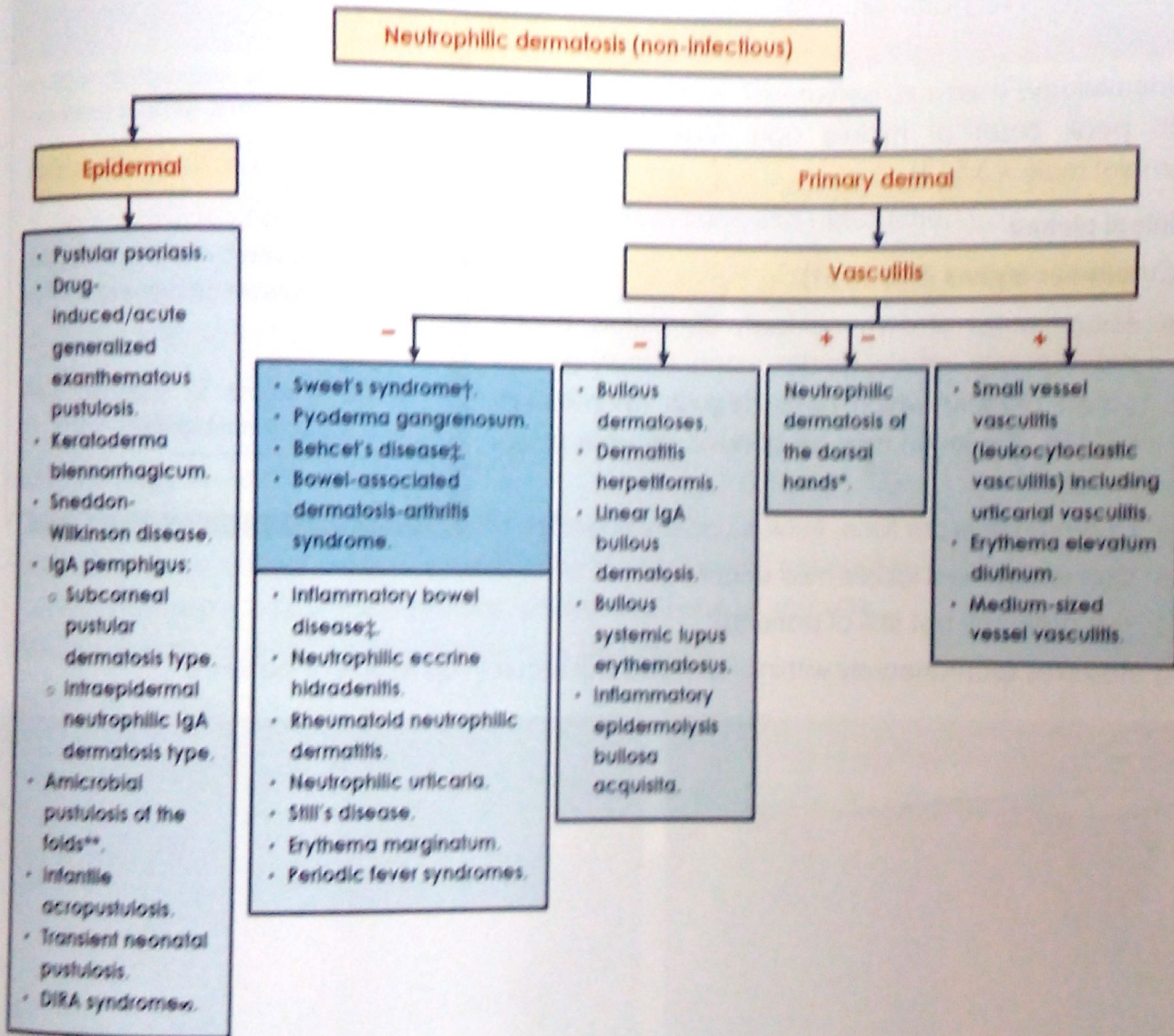
Behçet's disease

- A multisystem, polysymptomatic disease.
- Diagnosis is based on International Study Group criteria of recurrent oral ulceration, recurrent genital ulceration, ocular abnormalities (e.g. uveitis, retinal vasculitis) & cutaneous lesions.
- Cutaneous findings range from sterile papulopustules and palpable purpura to erythema nodosum-like lesions.
- Histologically, a neutrophilic angiocentric infiltrate with leukocytoclastic (early) or lymphocytic (late) vasculitis is the characteristic finding.

Neutrophilic Dermatoses

The neutrophilic dermatoses constitute a heterogeneous but linked spectrum of diseases, with significant overlapping histopathologic findings and similar pathogenic mechanisms & therapeutic approaches.

Non-infectious neutrophilic dermatoses



† Minority of patients have evidence of secondary vasculitic changes.

‡ Patients may have small vessel vasculitis.

* Localized neutrophilic dermatosis with pustules, hemorrhagic bullae & ulcers within erythematous nodules & plaques; dense dermal neutrophilic infiltrate > small vessel vasculitis; some authors consider it a subset of Sweet's syndrome.

** Chronic pustular dermatosis that primarily affects intertriginous sites, the external auditory canals & the scalp of young women with an autoimmune connective tissue disease, including systemic lupus erythematosus.

* Also neutrophilic infiltrate.

DIRA: Deficiency of the Interleukin-1 Receptor Antagonist.

Adapted mainly from: Bologna et al., Dermatology Textbook, Third edition, 2012.

Acute febrile neutrophilic dermatosis "Sweet's syndrome"²

The syndrome is characterized by red tender nodules or plaques showing dense neutrophilic dermal infiltrate without vasculitis, fever, elevated ESR, neutrophils with frequent involvement of extracutaneous tissue (as joints, kidneys and eyes) and dramatic response to systemic steroids.

Epidemiology: It occurs between 7 weeks to 85 years with peak onset at middle age. Mainly in women (female: male = 3.5 : 1).

Clinical picture

• Cutaneous lesions (Figs 58-61):

- Abrupt onset of asymmetrically distributed, bright-red to purple, painful tender, warm, sharply demarcated plaques which have irregular (mamillated) surface. The lesion may be annular, arcuate or ac-neiform.
- Common sites are face, trunk & upper extremities.
- Oral and genital lesions may occur.
- +ve pathergy test (8% of patients).
- Resolves spontaneously within 5-12 weeks but recurs in up to 30% of patients.

Proposed diagnostic criteria for Sweet's syndrome

Major criteria:

- Abrupt onset of tender or painful erythematous or violaceous plaques or nodules.
- Predominantly neutrophilic infiltration in the dermis without leukocytoclastic vasculitis.

Minor criteria:

- Preceded by fever or infection.
- Accompanied by fever, arthralgia, conjunctivitis or underlying malignancy.
- Leukocytosis.
- Good response to systemic steroids & not to antibiotics.

* *Cutis*, 1986; 37: 167-174.



Fig. 58. Sweet's syndrome

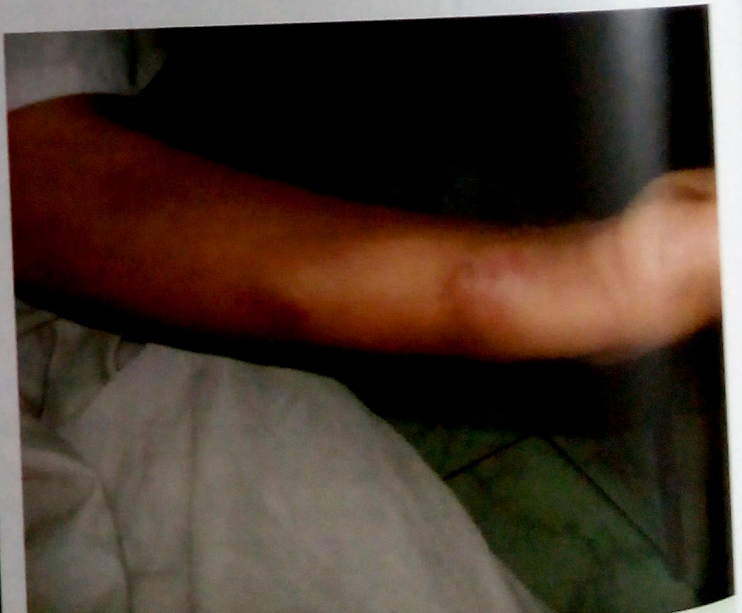


Fig. 59. Sweet's syndrome



Fig. 60. Sweet's syndrome



Fig. 61. Sweet's syndrome

Extracutaneous manifestations:

- o Serum sickness-like symptoms: Myalgia, nausea, malaise and headache.
- o Meningeal symptoms and GIT distress.
- o Arthralgia, arthritis of elbows and knees.
- o Renal affection 11-72%.
- o Red eye (iritis, conjunctivitis).
- o Neutrophilic alveolitis.

Histopathology

- There is upper and mid-dermal infiltration of neutrophils.
- The infiltrate less often includes: Lymphocytes, histiocytes and eosinophils.
- Leukocytoclasia is a prominent feature, without evidence of vasculitis.
- Dermal edema and RBCs extravasation may be present.

Laboratory findings (Fig. 62)

- $\uparrow$ ESR $\geq 90\%$, leukocytosis $>10,000/\text{mm}^3$.
- Neutrophilia $>70\%$.
- Antineutrophil cytoplasmic Abs (ANCA).

Request Date		12/12/2007	Sex	Female	Age	18 Y	Reporting date	13/12/2007
Complete Blood Picture								
Test	Result	Unit	Reference Range					
Hemoglobin Concentration	12.6	g%	(11.5 - 15.0)					
Haematocrit (PCV)	38.0	%	(35.0 - 45.0)					
Red Cell Count	5.11	million/cmm	(3.80 - 5.30)					
MCV	74.4	fL	(80.0 - 100.0)					
MCH	24.7	pg	(27.0 - 33.0)					
MCHC	33.2	g/dL	(31.0 - 37.0)					
RDW-CV	15.3	%	(11.5 - 15.0)					
Platelet Count	441	thousand/cmm	(150 - 450)					
Total leucocyte count	22.1	thousand/cmm	(4.0 - 11.0)					
Other cells								
Differential Leucocyte Count								
	Percentage	Absolute	Reference Range					
Neutrophils	77 %	17.02 $\times 10^9/L$	(40 - 80)					
Staff neutrophils	3 %	0.66 $\times 10^9/L$						
Seg. neutrophils	74 %	16.35 $\times 10^9/L$	(40 - 80)					
Lymphocytes	14 %	3.09 $\times 10^9/L$	(1.00 - 4.00)					
Monocytes	8 %	1.77 $\times 10^9/L$	(0.00 - 1.00)					
Eosinophils	1 %	0.22 $\times 10^9/L$	(0.00 - 0.50)					
Basophils	0 %	0.00 $\times 10^9/L$	(0.00 - 0.10)					
Comment: RBC'S SHOW HYPOCHROMIA, MICROCYTOSIS & ANISOCYTOSIS. MARKED PMN LEUCOCYTOSIS. RELATIVE LYMPHOPENIA. E.S.R. & CRP ARE RECOMMENDED.								

Fig. 62. CBC in Sweet's syndrome

Pathogenesis

- Ig and complement-mediated activation and mobilization of neutrophils.
- Antigen or superantigen-induced T-cell dependent cellular immune reactions.
- Local or systemic dysregulation of cytokine secretion, involving interleukin (IL)-1, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF) and interferon- γ .
- Association with HLA BW54.
- Altered function of neutrophils due to a heat-stable, non-lipid serum factor that enhances PNL migration.

Conditions reported in association with Sweet's syndrome

The syndrome has been described in association with a large number of diseases and may be preceded by infections, most commonly upper respiratory infections.

Malignant

- Acute myelogenous leukemia.
- Acute lymphocytic leukemia.
- Lymphoma.
- Breast cancer.
- Ovarian cancer.
- Vaginal cancer.
- Rectal cancer.
- Chronic myelogenous leukemia.
- Chronic lymphocytic leukemia.
- Myelodysplastic syndromes.
- Prostate cancer.
- Endometrial cancer.
- Testicular cancer.

Inflammatory

- Ulcerative colitis.
- Bowel bypass syndrome.
- Rheumatoid arthritis.
- Behçet's syndrome.
- Pyoderma gangrenosum.
- Cirrhosis.
- Crohn's disease.
- Sjögren's syndrome.
- Dressler's syndrome.
- Subacute thyroiditis.

Infections

- Staphylococcus.
- Yersinia.
- Tuberculosis.
- Meningitis.
- HIV.
- Streptococcus.
- Salmonella.
- Histoplasmosis.
- Hepatitis.

Others

- Drugs.
- Pregnancy.
- Renal stones.
- Immunizations.
- Photoinduction.

Characteristic features of malignancy associated Sweet's syndrome

HL

- Prior upper respiratory infection or other associated conditions uncommon.
- No sexual predilection.
- More severe cutaneous lesions.
- Cutaneous lesions often precede the diagnosis of malignancy (2/3).
- Occasionally hemorrhagic bullae and ulceration.

- Extracutaneous involvement in $\geq 50\%$ of patients.
- Absence of neutrophilia in $\geq 50\%$.
- Frequent anemia and abnormal platelet counts.
- High rate of recurrence (70%) often heralds tumor relapse.

Treatment

- Prednisone 40-60 mg/day (0.5 - 1.5 mg/kg/day), tapering over 4 to 6 weeks.
- Others: Potassium iodide, cyclosporine (5-10 mg/day - it decreases IL-1 production), colchicine (1.5 mg/day), clofazimine (200 mg/day), isotretinoin, methotrexate, dapsone (100-200 mg/day), indomethacin (50 mg/day).

Acute febrile neutrophilic dermatosis is a misnomer?



- Chronic recurrent forms exist.
- Fever and neutrophilia are variable features.
- Extracutaneous manifestations are common.

Behçet's disease "BD" (Hulusi Behçet, 1937)²

BD is a chronic multisystem disease characterized by oral & genital aphthae, arthritis, cutaneous lesions, ocular, gastrointestinal and neurologic manifestations. It must be differentiated from complex aphthosis which is characterized by the presence of almost constant, multiple (≥ 3) oral, or oral & genital aphthae, in the absence of systemic manifestations.

What are the neutrophilic dermatoses associated with bowel disorders?

- Behçet's disease.
- Bowel-associated dermatosis arthritis syndrome.
- Inflammatory bowel disease.

Epidemiology

BD affects individuals of Mediterranean origin and the Japanese more frequently. There is a significant association between HLAB51 and Behçet's disease, but there is no linkage between Behçet's disease and HLA-B27.

- Males > females in Middle Eastern countries.
- All ages including neonate with peak is between 20 and 35 years of age.

International study group criteria for the diagnosis of BD (1990)

Recurrent oral ulceration	Minor aphthous, major aphthous or herpetiform ulceration that recurred at least 3 times in one 12-month period.
Plus 2 of the following criteria:	
• Recurrent genital ulceration	Aphthous ulceration or scarring.
• Eye lesions	Anterior uveitis, cells in vitreous on slit lamp examination, or retinal vasculitis observed by ophthalmologist.
• Skin lesions	Erythema nodosum, pseudofolliculitis or papulopustular lesions; or acneiform nodules in post-adolescent patients not receiving corticosteroid treatment.
• Positive pathergy test	Read by physician at 24-48 hrs.

Pathergy test is performed on the flexor forearm by obliquely inserting a 20-22 gauge sterile hypodermic needle to a depth of 5 mm $\pm$ an intradermal injection of 0.1 ml of normal saline. A positive reaction is defined as the development of a papule or pustule.

Clinical manifestations

1) Mucocutaneous involvement

- **Recurrent aphthous stomatitis (RAS)** (Figs 63-66) 90-100% commonly occurs in the buccal mucosa, gums, tongue, lips and pharynx. Usually painful, 1-3 cm in diameter, shallow or deep and has a yellow fibrinous base. It may be single or multiple lasting from 1 to 4 weeks. Ulcers may be herpetiform with pin-point lesions occurring in coalescing clusters. Healing occurs without scarring.
- **Recurrent painful genital ulcers** (64-88%) (Figs 67-69), unlike the oral ulcers, genital ulcers tend to heal with scars.

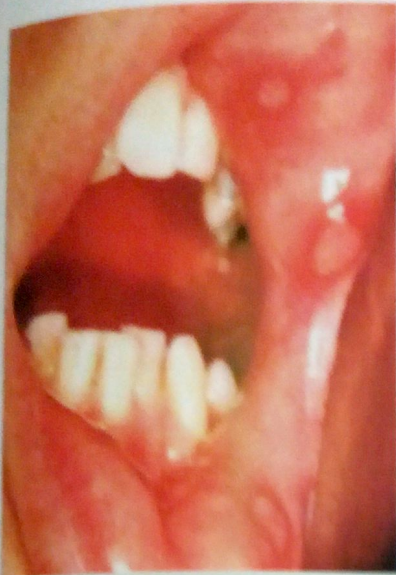


Fig. 63. Behçet's disease



Fig. 64. Behçet's disease



Fig. 65. Behçet's disease



Fig. 66. Behçet's disease



Fig. 67. Behçet's disease



Fig. 68. Behçet's disease

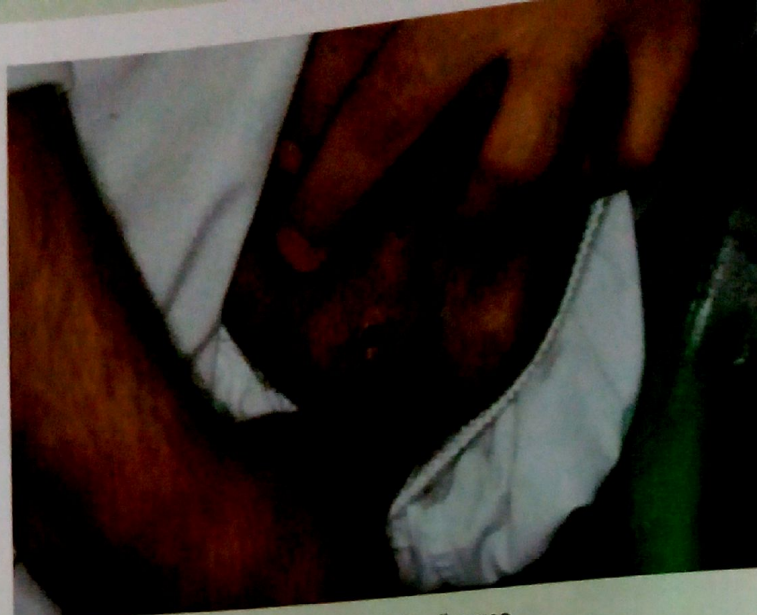


Fig. 69. Behçet's disease

- **Cutaneous lesions:** Papules, pustules, acneiform eruptions and tender nodules on the legs. It is a form of panniculitis different from that of EN (erythema nodosum-like). Increased reactivity of the skin to scratches and intracutaneous needle punctures "pathergy" occurs in 40-90% of patients and is manifested as self-healing sterile pustules.

II) Systemic manifestations of Behçet's disease:

Ocular (leading cause of morbidity)	Neurologic
• Occurs in 90% of patients; favors men, in whom it is more severe. • Can be painful & may lead to blindness. • Retinal vasculitis (more frequently associated with blindness). • Posterior uveitis (most characteristic ocular finding). • Anterior uveitis, hypopyon. • Secondary glaucoma, cataracts. • Conjunctivitis, scleritis, keratitis, vitreous hemorrhage, optic neuritis.	• Usually appears later during the evolution of the disease. • Associated with a poor prognosis. • Acute meningo-encephalitis which may resolve spontaneously. • Cranial nerve palsies. • Brainstem lesions that can induce swallowing difficulties, laughter & crying. • Pyramidal or extrapyramidal signs.
Joints	Gastrointestinal
• Approximately 50% of patients develop arthritis. • In majority (~80% of patients), duration of attacks is <2 months. • Mono- or poly-arthritic & non-erosive. • Most commonly knees, wrists & ankles.	• Abdominal pain &/or hemorrhage may be difficult to distinguish from IBD. • Ulcerations* develop within the small bowel (in particular the ileocecal region) as well as the transverse & ascending colon and esophagus; perforation can occur.
Vascular	Cardiopulmonary
• Aneurysmal or occlusive arterial disease. • Superficial or deep venous thrombosis.	• Coronary arteritis, valvular disease, myocarditis. • Recurrent ventricular arrhythmias. • Pulmonary artery aneurysms.
Renal	
• Glomerulonephritis.	

* Resemble anogenital aphthae.

Neonatal Behçet's disease has been reported in all whose mothers were affected with BD. At birth, the infants had oral or genital ulceration along with pustules and necrotic skin ulcerations in the periungual distribution. In all babies, the disease is self-limited within 6 weeks, but may be severe, presenting with bloody diarrhea, severe orogenital ulcers, progressing to stridor and respiratory arrest. Oral and genital ulcers, cutaneous lesions, arthritis & uveitis are common clinical manifestations of childhood BD.

Course

Related to the degree of major organs involvement, with higher mortality in CVS and CNS affection.

Histopathology

The pathologic changes common to the various organs affected by BD are vasculitis and thrombosis. Early lesions reveal leukocytoclastic vasculitis.

Pathogenesis

- **Genetic background:** Suggested by its association with HLA-B51.
- **Infectious etiology:** Some infections may potentially trigger an immunoregulatory defect in the genetically predisposed. Among the infectious agents investigated were HSV, hepatitis C virus, parvovirus B19 and more recently, streptococcal strains.
- **Autoimmune responses:**
 - Circulating immune complexes: Patients with Behçet's disease had to have a significantly higher number of circulating immune complexes.
 - Role of neutrophils: There is enhanced neutrophil chemotaxis, activation and production of ROS and lysosomal enzymes → tissue injury.
 - Role for cytokines is also suggested & the levels of cytokines IL-12 (promotes a Th1 response) and IL-8 (a neutrophil chemoattractant) correlate with disease activity.
 - Clonal expansion of autoreactive T-cells that recognize a peptide derived from heat shock protein 60 has also been described.
- High prevalence of procoagulant mutations and increased platelet activation has also been suggested as an explanation for the thrombotic component of the disease.

Treatment of Behçet's disease

Treatment	Dose
Mucocutaneous disease	
Viscous lidocaine, topical sucralfate & other symptomatic treatments.	
Topical & inhalant corticosteroids.	
Intralesional corticosteroids.	
Colchicine.	0.6 mg po thrice daily.
Dapsone.	50-150 mg po daily (or sulfapyridine equivalent).
Combination oral colchicine & dapsone.	
Severe mucocutaneous disease	
Thalidomide.	50-150 mg po nightly.
Methotrexate.	2.5-25 mg po or IM weekly.
Prednisone, intermittent with taper.	40-80 mg po daily usual starting dose.
Interferon- α -2a.	Variable dose ($3-9 \times 10^6$ IU SC 3x weekly).
TNF- α inhibitors (e.g. etanercept, infliximab).	
Systemic disease	
Prednisone.	60-120 mg po daily usual starting dose (including split-dose), with taper to alternate days.
Methylprednisolone acetate.	40 mg IM 3x weekly.
Azathioprine.	50-100 mg po twice daily.
Cyclophosphamide.	Variable oral dose (50-200 mg daily) or IV pulse (500-1000 mg monthly then 500-1000 mg every 3 months).
Chlorambucil.	4-6 mg po daily.
Mycophenolate mofetil.	1-1.5 g po twice daily.
Cyclosporine.	Variable doses (2-10 mg/kg po daily).
Tacrolimus.	0.1-0.2 mg/kg po daily.
IVIg.	2-3 g/kg IV monthly (given over 2-5 consecutive days).
TNF- α inhibitors (e.g. etanercept, infliximab).	

Differential diagnosis of Behçet's disease

1) Oculomucocutaneous syndromes:

Disease	Main lesions		
	Oral & genital	Ocular	Skin
Behçet's syndrome	Aphthae	Uveitis	Erythema nodosum
Sweet's syndrome	Aphthae	Conjunctivitis episcleritis	Inflamed papules or nodules
Erythema multiforme	Erosions	Erosions	Target lesions
Cicatricial pemphigoid	Bullae, erosions	Erosions, erosions	Occasional dome-shaped bullae
Pemphigus	Erosions	Erosions	Multiple flaccid bullae
Reiter's syndrome	Ulcers	Conjunctivitis	Keratoderma blennorrhagica

Other oculomucocutaneous syndromes: Ulcerative colitis, herpes simplex, syphilis, LE, MCTD.

II) Common causes of oral ulcers²

- **Local causes** "traumatic", e.g. orthodontic appliances.
- **Recurrent aphthous stomatitis** "RAS" and Behçet's disease*.
- **Malignant neoplasms** – oral SCC (Fig. 70).
- **Ulcers associated with systemic disease:**
 - Blood disorders: Anemia, leukemia, neutropenia.
 - GIT disease: Coeliac disease, Crohn's disease, ulcerative colitis.
 - Rheumatic diseases: LE, Reiter's disease*, Sweet's syndrome.
 - Cutaneous disease: Erosive lichen planus (Fig. 71), pemphigus (Fig. 72), pemphigoid, erythema multiforme* (Fig. 73), DH, epidermolysis bullosa.
 - Vasculitis: PAN, Wegener's granulomatosis.
- **Microbial diseases:** Herpetic stomatitis*, chicken pox, herpes zoster, hand foot and mouth disease, herpangina, infectious mononucleosis, acute necrotizing gingivitis, tuberculosis, syphilis, AIDS.
- **Drug-induced:**
 - Cytotoxic agents, e.g. methotrexate.
 - Acrodynia: Mercury poisoning.

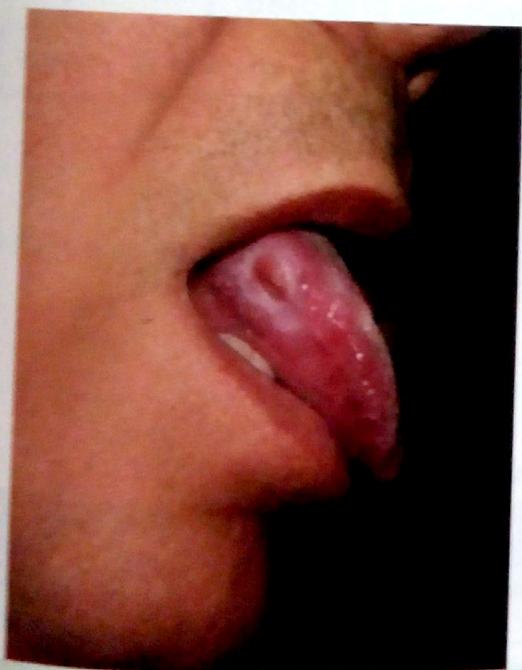


Fig. 70. SCC



Fig. 71. Oral lichen planus



Fig. 72. Pemphigus vulgaris



Fig. 73. Erythema multiforme minor

Recurrent aphthous stomatitis "RAS" ¹

RAS is the most common ulcerative disease of the oral cavity affecting at least 20% of the population. It is characterized by recurring episodes of small, round or ovoid ulcers with a circumscribed margin, erythematous halo & a yellow or grey floor, each lasting from 1-4 weeks before healing.

Etiology of RAS is obscure. Different predisposing factors have been proposed.

- Behçet's disease.
- Hematological deficiencies (10-20%), e.g. iron, folic acid, Vit. B12.
- Malabsorption states, e.g. coeliac disease, Crohn's disease.
- Trauma, certain foods, stress and cessation of smoking may play a role.

There is no evidence that RAS is an autoimmune disease. However, CMI mechanisms may be involved in the pathogenesis of RAS.

Clinical features

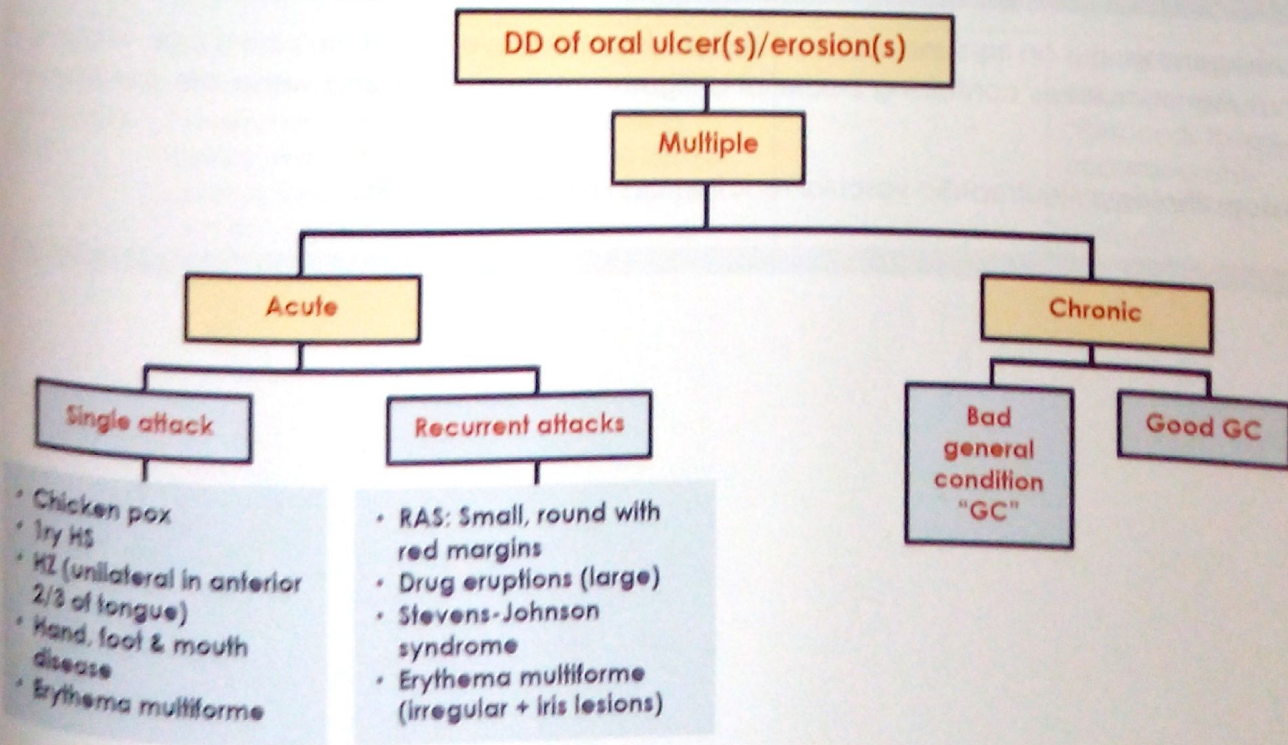
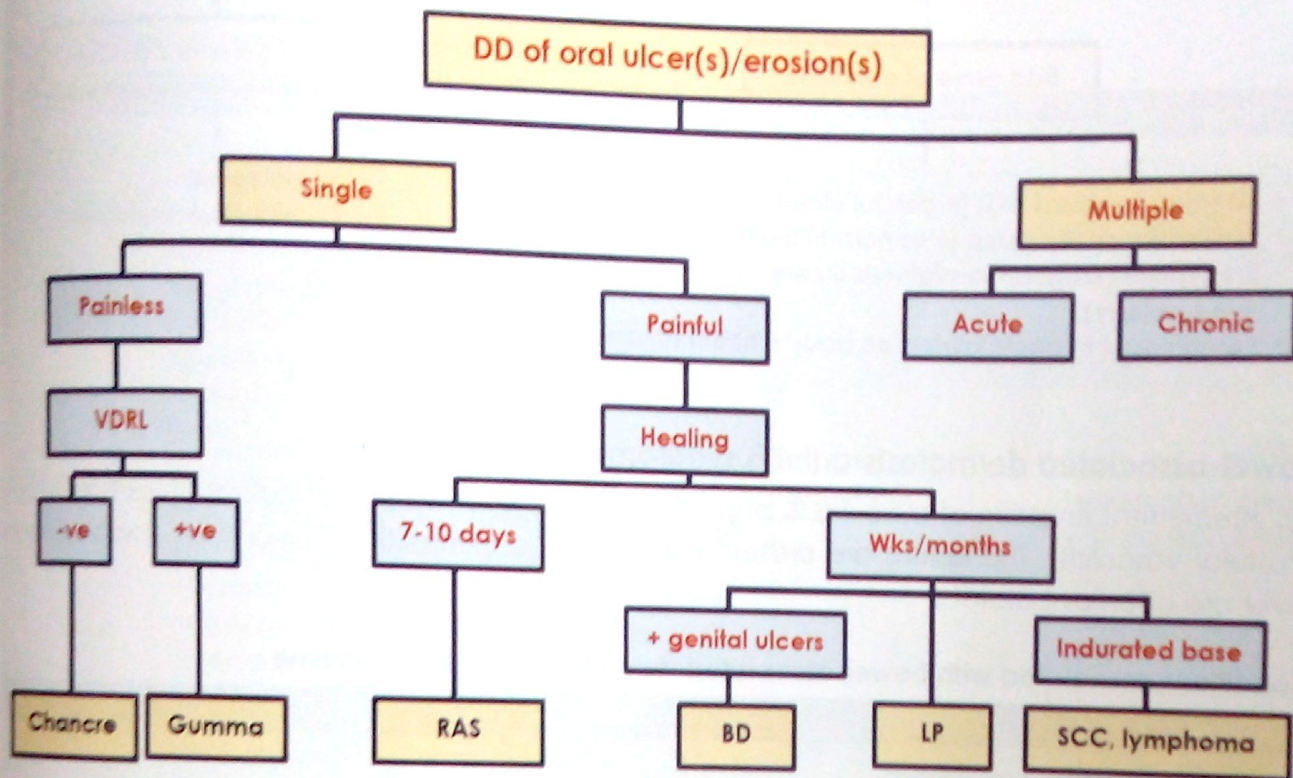
3 main clinical types:

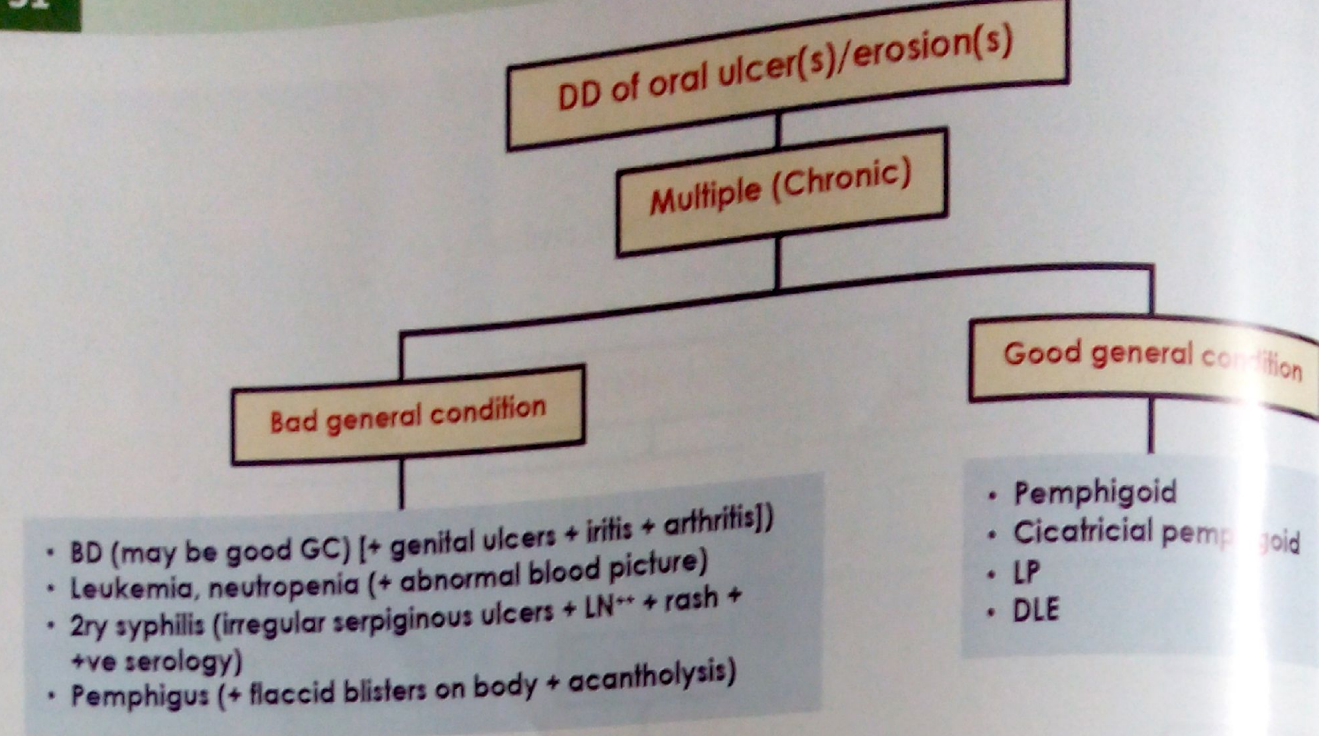
Characteristics of the three variants of recurrent aphthous stomatitis

Characteristic	Ulcer type		
	Minor aphthous	Major aphthous	Herpetiform
Female: male ratio	1.3:1	0.8:1	2.6:1
Age of onset	Childhood or adolescence		Young adult
Lesions			
• Size	<10 mm	>10 mm	1-2 mm
• Site	Lips, cheeks, tongue	Lips, cheeks, tongue, palate, pharynx	Entire oral mucosa
Number	1-5		10-100
Duration of each ulcer	Up to 10 days	1-3	Up to 1 month
Healing with scarring	10%	Up to 1 month	Up to 1 month
Prevalence	80% "most common"	65%	30%
		10%	10%

Treatment of RAS

- Exclude systemic diseases.
- Treatment of predisposing factors.
- Topical: Tetracycline mouth wash or topical steroids in orabase 4 times daily.
- Thalidomide 300 mg daily, dapsone, colchicine.





Bowel-associated dermatosis-arthritis syndrome

An intermittent eruption of macules & papules that may evolve into vesiculopustules & necrosis (Pustular vasculitis). The lesions are present mainly on the extremities. Polyarthritis, malaise, and fever are often associated.

Conditions associated with bowel-associated dermatosis-arthritis syndrome

Surgical	Medical
• Gastric resection. • Jejunioileal bypass. • Blind loops of bowel following surgery. • Biliopancreatic diversion.	• Inflammatory bowel disease. • Diverticulitis. • Peptic ulcer disease.

Pathogenesis: It is an immune complex disease (bacterial overgrowth in a blind loop of bowel → immune complexes containing bacterial antigens are then deposited within the skin & synovium).

Histopathology: Neutrophilic vascular reaction as in Behçet's disease.

Pyoderma gangrenosum (PG)²

Definition: PG is a destructive, necrotizing, non-infective ulceration of the skin, affecting mainly adults between 25 and 54 years. It can occur in childhood, usually in association with a systemic disease such as IBD, immunodeficiency, immunosuppression, leukemia or HIV infection. In adults, it may occur in otherwise healthy persons or in association with systemic disease.

Classification of pyoderma gangrenosum

Variant	Clinical	Histopathologic	Associated disease	Treatment
Ulcerative "Classic" (Figs 74-76)	Painful ulceration with well-defined blue undermined borders & surrounding erythema purulent base often rapidly enlarges. Site: Mainly lower limbs or trunk.	Centrally, neutrophilic abscess. Distally, lymphocytic angiocentric infiltrate (Figs 77-79).	IBD, arthritis, monoclonal gammopathy.	Aggressive immunosuppressive therapy.
Pustular	Discrete painful pustules (2-8 mm) on normal skin with inflammatory border, mainly on extensor aspects of extremities or upper trunk.	Subcorneal pustules; perifollicular & dermal dense neutrophilic infiltrates with subepidermal edema.	Acute IBD.	Lesions often clear with control of IBD.
Bullous "Atypical"	Superficial painful bulla with progressive evolution erosion & ulceration with surrounding erythema.	Subepidermal bulla, dermal neutrophilic infiltrate, intraepidermal vesiculation.	Myeloproliferative disorders.	Systemic immunosuppressive therapy.
Vegetative "Superficial granulomatous"	Superficial ulcer without undermined border, nonpainful, solitary, slowly progressive may be exophytic vegetative.	Pseudoepitheliomatous hyperplasia, sinus tracts, palisading granuloma & dermal neutrophilic abscess.	No associated diseases.	Topical or intralesional steroids "Responds to less aggressive anti-inflammatory therapy".



Fig. 74. Pyoderma gangrenosum



Fig. 75. Pyoderma gangrenosum



Fig. 76. Pyoderma gangrenosum

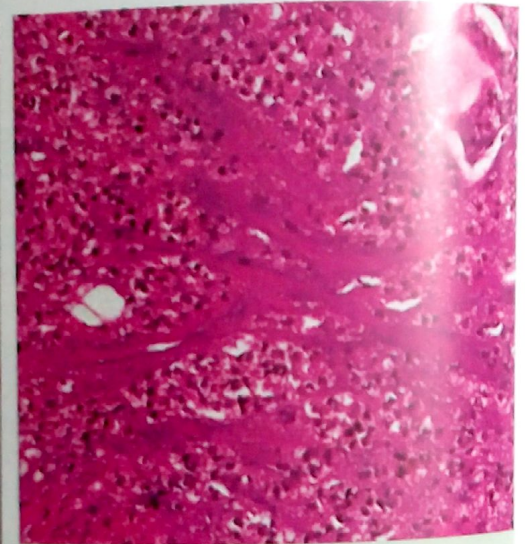


Fig. 77. Histopathology of pyoderma gangrenosum

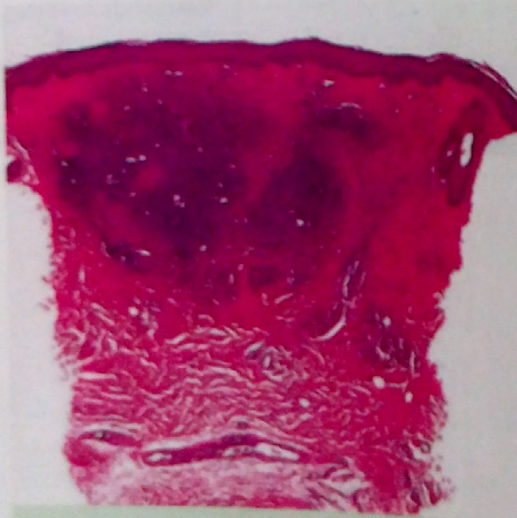


Fig. 78. Histopathology of pyoderma gangrenosum

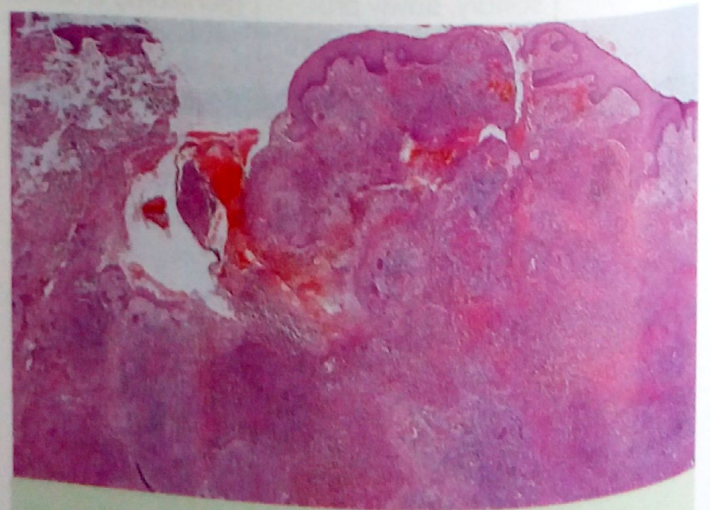


Fig. 79. Histopathology of pyoderma gangrenosum

Pyostomatitis vegetans

- Chronic, vegetative, sterile pyoderma of the labial and buccal mucosa.
- May be associated with vegetative or ulcerative cutaneous PG.
- Seen in patients with inflammatory bowel disease.

The pathergic phenomenon: Localized PG to sites of skin damaged by trauma, surgery, or venopuncture, may represent a localized, misdirected, host-mediated antigenically changed by trauma in a patient with altered immune reactivity.

Proposed diagnostic criteria for classic ulcerative pyoderma gangrenosum.

Major criteria

- Rapid^a progression of a painful^b, necrolytic cutaneous ulcer^c with an irregular, violaceous & undermined border.
- Other causes of cutaneous ulceration have been excluded^d.

Minor criteria

- History suggestive of pathergy^e or clinical finding of cribriform scarring.
- Systemic diseases associated with pyoderma gangrenosum^f.
- Histopathologic findings (sterile dermal neutrophilia, $\pm$ mixed inflammation, $\pm$ lymphocytic vasculitis).
- Treatment response (rapid response to systemic corticosteroids)^g.

Diagnosis requires both of the major criteria and at least two minor criteria.

^a Characteristic margin expansion of 1-2 cm per day, or a 50% increase in ulcer size within 1 month.

^b Pain is usually out of proportion to the size of the ulceration.

^c Typically preceded by a papule, pustule or bulla.

^d Usually necessitates skin biopsy & additional evaluation to exclude other causes.

^e Ulcer development at sites of minor cutaneous trauma.

^f Inflammatory bowel disease, arthritis, IgA gammopathy, or underlying malignancy.

^g Generally responds to prednisone (1-2 mg/kg/day) or another corticosteroid at an equivalent dosage, with a 50% decrease in size within 1 month.

Adapted mainly from: Bolognia et al., Dermatology Textbook, Third edition, 2012.

Associated diseases (50% of patients)

- **Inflammatory bowel disease (IBD):** In 1/3 of patients with ulcerative and pustular PG. Both chronic ulcerative colitis and Crohn's disease occur with equal frequency.
- **Arthritis:** 37% of patients with ulcerative PG.
- **Immunologic abnormalities:** Both humoral and cell-mediated immune defects, e.g. congenital and acquired hypogammaglobulinemia, hyperimmunoglobulin E syndrome, cutaneous anergy to purified protein derivative, defective neutrophil function.
- **Monoclonal gammopathy:** 10% of patients with PG most often of IgA type & is usually benign. The average age of patients with PG and gammopathy is older than that of those without gammopathy.
- **Malignancy:** e.g. leukemia and acute or myeloid leukemia, myeloma.

Malignant pyoderma: An aggressive variant of ulcerative PG in the head and neck. It doesn't have the livid rim or necrotic center of classic type. ANCA may be a marker of the syndrome.

Management

- **Generally:**
 - Exclude any local and systemic disease associated with PG.

- Debridement of the ulcer by saline solution, 0.5% silver nitrate.
- Hydrophilic antimicrobial agents.

Treatment of pyoderma gangrenosum (Fig. 80)

Treatment	Dose
Inflammatory disease	
Mild disease &/or adjunctive therapy	
Superpotent topical corticosteroids	
Intralesional corticosteroids	
Topical tacrolimus	
Oral antibiotics (e.g. sulfonamides, minocycline)	
Colchicine	0.6 mg po thrice daily
Dapsone	50-150 mg po daily.
Combination colchicine/dapsone	
Clofazimine	100-400 mg po daily
Other (e.g. oral potassium iodide, intralesional cyclosporine, topical cromolyn sodium, nicotine patch or cream)	
More severe disease	
Prednisone	60-120 mg po daily usual starting dose (including split-dose), with taper to alternate days.
Methylprednisolone	1 g daily for 3-5 days (IV pulse)*
Thalidomide†	50-100 mg po nightly.
Cyclosporine	2.5-5 mg/kg po daily.
Tacrolimus	0.1-0.2 mg/kg po daily.
TNF- α inhibitors‡	Infliximab 5 mg/kg IV at weeks 0, 2 & 6; adalimumab 80 mg SC as initial dose then 40 mg SC weekly or every other week; etanercept 50-100 mg SC weekly (in 1 or 2 doses).
Methotrexate**	2.5-25 mg po or IM weekly.
Azathioprine**	50-100 mg po twice daily.
Mycophenolate mofetil**	1-1.5 g po twice daily.
Chlorambucil	4-6 mg po daily.
IVIg	2-3 g/kg IV monthly (given over 2-5 consecutive days).
Granulocyte apheresis, plasmapheresis	
Total colectomy (severe chronic ulcerative colitis)	
Non-inflammatory disease	
Bio-occlusive dressings	
Compression, limb elevation	

* Followed by daily oral prednisone.

† Especially in patients with Behçet's disease.

‡ Especially in patients with inflammatory bowel disease.

§ 50-70% response rate.

** Often used in combination with other agents or as maintenance therapy.

Adapted mainly from: Bologna et al., *Dermatology Textbook*, Third edition, 2012.



Fig. 80. Pyoderma gangrenosum before & after treatment with systemic steroids and azathioprine

Malignant atrophic papulosis "Degos disease"

It is usually a fatal disease characterized by an endovasculitis of the skin, GIT, and occasionally other viscera. It commonly affects young men.

Pathogenesis: A viral agent has been suggested. It should not be considered as vasculitis, since there is little inflammation of the vessel wall and immune complexes have not been detected. An impaired endothelial function or abnormalities of coagulation may be the cause.

Clinical features

- **Cutaneous lesions:** Crops of asymptomatic erythematous papules that gradually develop an atrophic porcelain-white center. The lesions commonly affect trunk and extremities (mainly proximal portions). The bulbar conjunctiva and the oral mucosa may be involved.
- **Systemic manifestations:** Appear few months after the onset of the cutaneous lesions in the form of recurrent attacks of abdominal pain, nausea, vomiting and colics due to gut affection. Death occurs from intestinal hemorrhage, or perforation or from cerebral infarctions. In some of the patients who have cutaneous lesions only (4%), cutaneous LE must be ruled-out.

Histopathology: Endothelial swelling and thrombosis of small arteries with absent inflammation in vessel wall. A wedge-shaped area of necrosis of the dermis in which the collagen appears homogeneous and devoid of nuclei. Mucin deposits are found in the area of necrosis. The stratum malpighii is markedly atrophic.

EM: Intracytoplasmic tubular aggregate "paramyxoma-like bodies" have been found.

Treatment: Phenylbutazone, fibrinolytic therapy. Aspirin and dipyridamide may be effective.

Cutaneous-intestinal syndrome

May simulate Degos disease as it is a combination of macular, blistering and crusting lesion with oropharyngeal ulceration. Death occurs from perforation. It differs histologically from Degos disease by extensive infiltration in the dermis composed mainly from histiocytes, PMNL and lymphocytes.

Livedo reticularis¹

It is a cyanotic, mottled discoloration of the skin, with a characteristic network pattern which is accentuated by cold. Cutis marmorata: Is the physiologic transitory mottling of the skin observed on cold exposure in 50% of normal children or adults. Livedo reticularis, in contrast, is persistent and unresponsive to rewarming.

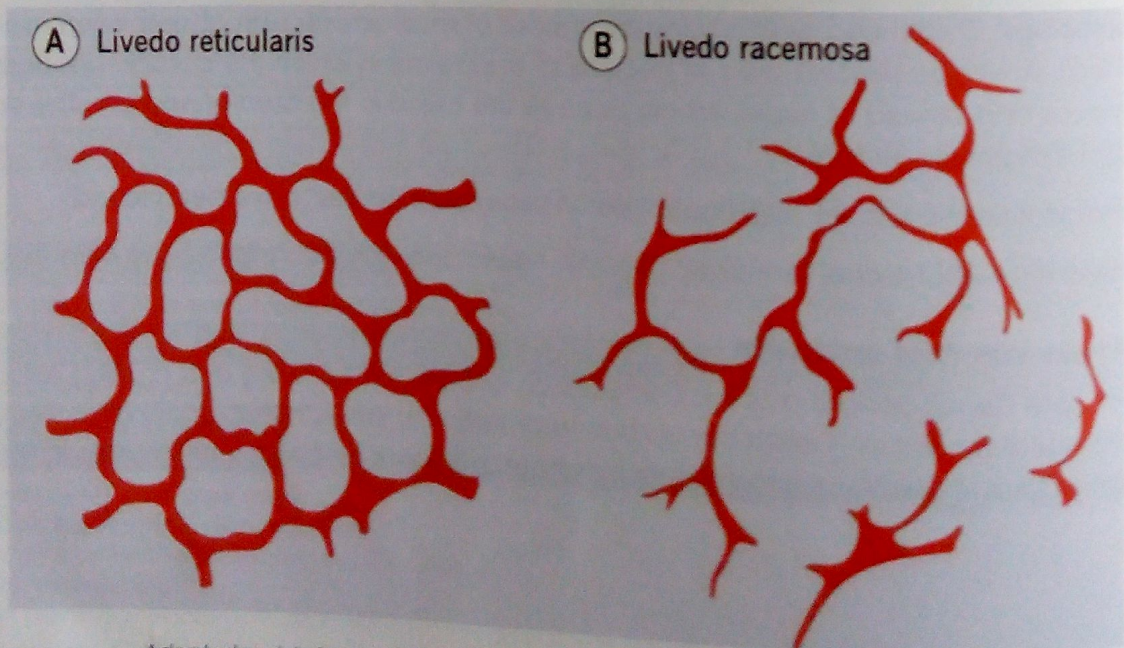
Pathogenesis: The blood supply of normal skin is arranged in cones, their bases 1-4 cm across on the surface of skin, each supplied by an arteriole. The mottling of livedo reticularis follows this pattern. The color changes is due to dilatation of, and stagnation within, the capillaries and minute venules in the dark areas.

The clinical pattern of LR can vary with the nature of the underlying cause:

- **A complete fine network:** Indicates alterations in blood flow caused by vasospasm or by factors within the blood that alter the viscosity and the flow through the vessels.
- **Patchy distribution:** Indicates vessel wall pathology and intraluminal obstruction.
- **Livedo racemosa:** Distinct pattern of LR consisting of a large branching pattern that is usually situated on the trunk and proximal limbs. It is indicative of Sneddon's syndrome or antiphospholipid antibody syndrome (APS).

Causes of Livedo reticularis

- Physiological: Cutis marmorata.
- Intravascular obstruction:
 - Emboli: Cholesterol.
 - Hypercoagulopathy: Disseminated intravascular coagulation & antiphospholipid syndrome.
 - Paraproteinemia: Cryoglobulinemia & cold agglutinin.
- Vessel wall disease:
- Arteriosclerosis.
- Metabolic: Hyperparathyroidism, hypercalcemia.
- Arteritis:
 - Vasculitis: e.g. polyarteritis nodosa & atrophie blanche.
 - CT disease, e.g. LE, SS, DM, MCTD.
 - Infections: Syphilis, TB.
- Idiopathic.
- Congenital.
- Miscellaneous: Drugs, pancreatitis, capillary nevi.



Adapted mainly from: Bolognia et al., Dermatology Textbook, Third edition, 2012.

Sneddon's syndrome: Extensive livedo reticularis and cerebrovascular disease, e.g. hemiplegia and aphasia.

Livedo with ulceration – Livedoid vasculitis "atrophie blanche – AB"

A smooth, ivory-white plaque of sclerosis stippled with telangiectases & surrounded by hyperpigmentation. It occurs mainly on the lower leg or foot in women (female: male = 4:1), in association with chronic venous insufficiency (CVI) (99%). It has been also noted in cryoglobulinemia, SLE and scleroderma.

Painful ulcers occur in about 30% of cases, within an area of livedo reticularis, that heal slowly, or precede the appearance of the lesions.

Histopathology: Similar to Livedo reticularis but more severe. There is endothelial swelling, intimal thickening and hyalinization, thrombosis, extravasation of RBCs, and mild perivascular lymphocytic infiltrate. The affected blood vessels are usually in mid-dermal location.

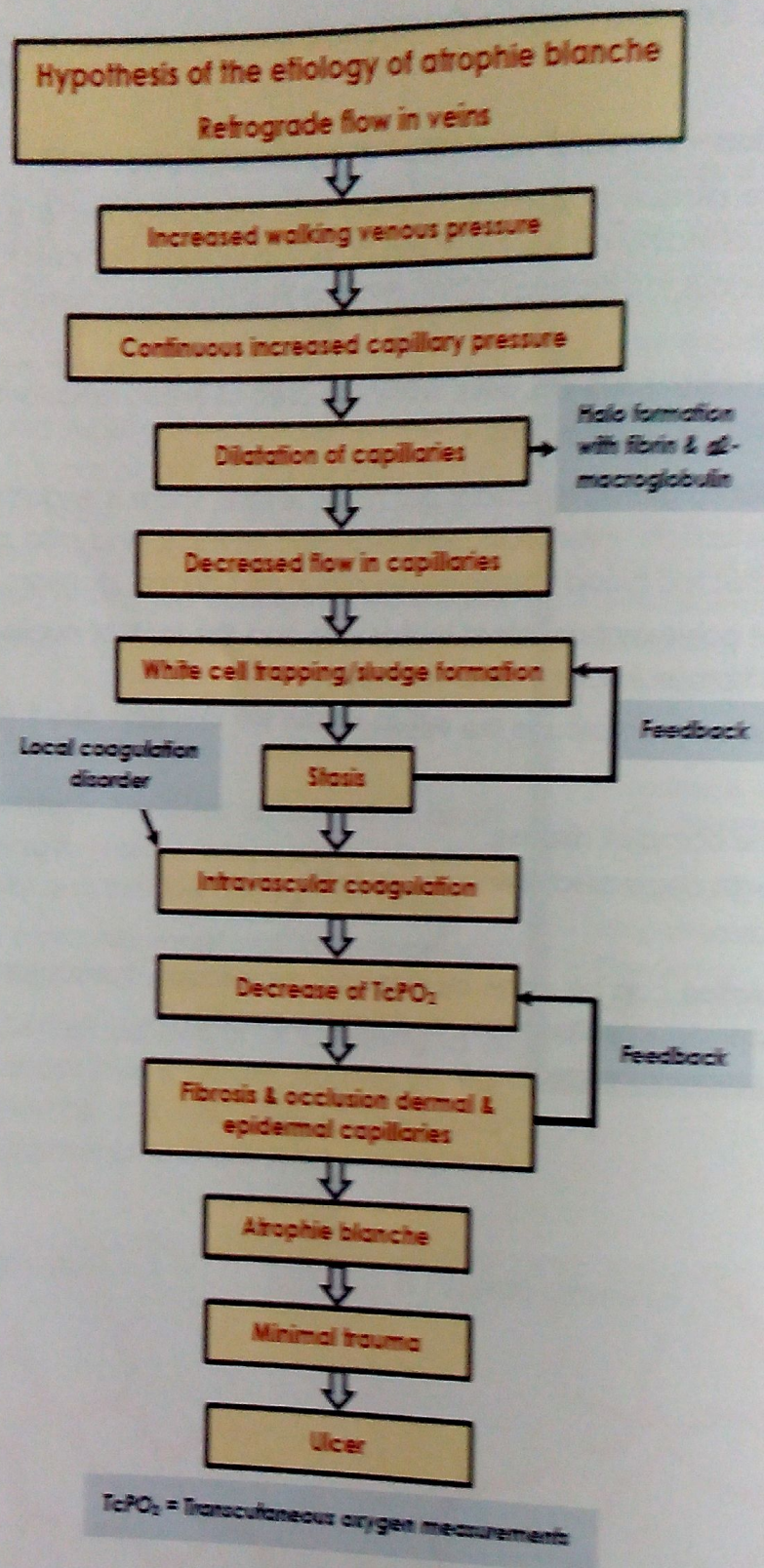
The small number of polymorphonuclear leukocytes and the lack of nuclear fragments help in differentiation of AB from leukocytoclastic vasculitis.

IgG, IgM and C3 can be seen around the vessels.

Pathogenesis:

- A localized immune complex disease.
- A coagulopathy with decreased fibrinolytic activity.
- A primary vasospasm.

Study of microcirculation can be done by capillary microscopy, transcutaneous oxygen measurement (TCPO₂), laser doppler flowmetry and lymphography.



Therapy

- Management of CVI by adequate compression therapy is the 1st choice treatment of AB.
- Drugs stimulating endogenous fibrinolytic activity:
 - Combination of phenformin + ethylestrenol → ↑ plasminogen activating enzymes but phenformin was removed from the general market due to its side effects.
 - Low dose of t-PA (tissue plasminogen activator).
 - Aspirin and warfarin.

• **Drugs inhibiting thrombus formation:**

- Aspirin and dipyridamole.
- Prostaglandin E.
- Pentoxifylline.
- Heparin.

• **Vasodilating drugs:**

- Nifedipine.
- Sulfasalazine.

Neutrophilic dermatoses with associated vascular changes

• **Leukocytoclastic vasculitis:**

- Small-vessel variants (necrotizing venulitis).
- Large-vessel variants.

• **Sweet's syndrome.**

• **Pustular vasculitis:**

- Behçet's disease.
- Bowel-associated dermatosis-arthritis syndrome.

• **Erythema nodosum.**

• **Pyoderma gangrenosum.**

• **Other:**

- Familial Mediterranean fever.
- Selected disseminated infections.

Non-venereal sclerosing lymphangitis "Phlebitis" of the penis HL

It is a benign self-limiting disorder, affecting sexually active men between the ages of 20 and 40.

Clinically: It is characterized by sudden appearance of painless, hard, translucent, cord-like, sub-cutaneous lesion partially encircling the penis in the coronal sulcus. Spontaneous resolution takes place in 2-6 weeks.

Histogenesis: The condition may be considered as simple dilatation of a lymph vessel, i.e. lymphangiectasis, or it may be a vein, due to the stain of endothelial cells with factor VIII-related antigen.

Treatment: Aspiration, leads to temporary resolution. Various anti-inflammatory and corticosteroid preparations have been used without beneficial effect.

Ulcers



- The history should include onset, course, symptoms, exacerbating and alleviating factors, past medical history, family history, social history, travel and medications.
- Important aspects of the physical examination include location, size and shape of the ulcer, characteristics of the ulcer edge and base, and associated physical findings.
- Helpful laboratory evaluation includes vascular studies, blood tests, cultures and biopsy.
- A biopsy of non-healing chronic ulcers is indicated to exclude carcinoma or other underlying diseases.
- **In addition to local care, therapy of ulcers should aim to correct or treat the underlying cause:**
 - Venous insufficiency: Compression.
 - Arterial insufficiency: Surgery.
 - Neuropathic or pressure ulcer: relief of pressure.
 - Infection: Antibiotics.
 - Neoplasm: Surgery, chemotherapy, radiotherapy.
 - Vasculopathy: Treat the underlying cause of the occlusive disorder.
 - Vasculitis or other inflammatory process (e.g. pyoderma gangrenosum): Corticosteroids, immunosuppressive agents.
- **A key factor in therapy is the promotion of wound healing:**
 - Debridement: Mechanical, enzymatic, autolytic.
 - Dressings: Maintain a moist wound environment.
 - Infection control: Antibiotics.
 - Skin grafting or skin substitutes.
 - Growth factors.

Leg ulcers²

Leg ulcers occur relatively commonly in late middle and old age, arising in association with chronic venous insufficiency (80% of cases), chronic arterial insufficiency (10-25% of cases), or peripheral sensory neuropathy, in some patients a combination of these factors.

Causes

- **Trauma:** Injuries, burns, cold injury, factitia, self-inflicted (dermatitis artefacta).
- **Infections:**
 - Viral.
 - Bacterial: Furuncle, ecthyma*, Gram -ve infections, anaerobic infections, mycobacterial.
 - Spirocheatal: Syphilis (gumma*), yaws.
 - Fungal: Majocchi's granuloma, deep fungal infections.
 - Protozoal: Leishmaniasis.
- **Metabolic:** Diabetes, gout.
- **Neuropathic**:** Diabetes, leprosy, tabes dorsalis, syringomyelia.
- **Vascular diseases:**
 - Venous**: Varicose veins, congenital absence of veins, post-thrombotic.
 - Arterial**: Atherosclerosis, hypertension, arteriovenous malformation, cholesterol embolism.
 - Vasculitis: Polyarteritis nodosa, Wegener's, rheumatoid, SLE, Behçet's disease, atrophie blanche, pyoderma gangrenosum*.
 - Lymphatics: Lymphedema.
- **Blood diseases:** Polycythemia, sickle-cell anemia, coagulopathy, cryoglobulinemias*.
- **Neoplastic*:** SCC, BCC, Kaposi's sarcoma, metastasis, leukemia, lymphoma and CTCL.
- **Panniculitis:** Weber-Christian disease, Necrobiosis lipoidica*, Weber-Christian disease.

Venous ulcers constitute the majority (80%) of all leg ulcers, whereas foot ulcers are more likely to be due to arterial insufficiency or neuropathy.

Points to include in the history & physical examination of patients with a leg ulcer

History	Physical examination
• Onset & clinical course of ulcer. • Symptoms, including those of vascular disease or neuropathy. • Alleviating factors. • Exacerbating factors. • Past medical history, e.g. diabetes mellitus, auto-immune CTD. • Family history. • Medications, topical & systemic. • Personal habits (e.g. smoking, alcohol intake).	General, emphasizing the following: • Ulcer characteristics: ◦ Location & size. ◦ Morphology, including depth, shape, border & base. ◦ Surrounding skin, e.g. edema, dermatitis, fibrosis, cellulitis, necrosis. • Peripheral pulses. • Capillary refill time. • Evidence of peripheral neuropathy. • Deep tendon reflexes.

* Common.

** Very common.

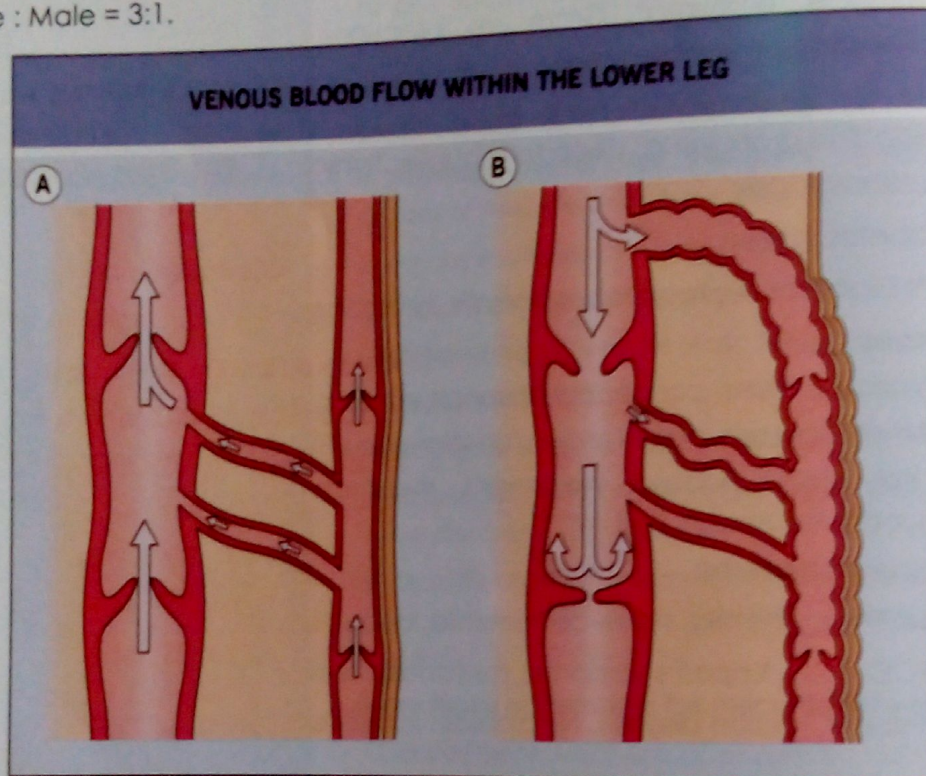
Chronic venous insufficiency "CVI" and varicose veins "VV"

CVI results from failure of return of venous blood and $\uparrow$ capillary pressure $\rightarrow$ edema, stasis dermatitis, hyperpigmentation, fibrosis of the skin and subcutaneous tissue (lipodermatosclerosis) of leg and ulceration.

VVs: Abnormal lengthening, dilatation and twisting of the superficial vessels associated with abnormal valvular function.

Epidemiology (VVs)

- Age of onset: 30-40 yrs.
- Sex: Female : Male = 3:1.



Venous blood flow within the lower leg. **A** Under normal circumstances. **B** When the valves are incompetent.

Bolognia et al., *Dermatology Textbook*, Third edition, 2012.

Pathogenesis of CVI (venous hypertension) & ulceration

- Dysfunction of valves in the superficial and/ or communicating and/or deep system due to congenital or acquired incompetence.
- Deep venous outflow obstruction (i.e. thrombus formation).
- Muscle dysfunction and calf muscle pump failure.

Several hypotheses have been proposed to explain the development of venous ulceration:

- Pericapillary fibrin cuffs and fibrinolytic abnormalities: Sustained venous hypertension within the venous system of the leg is transmitted to the capillary circulation $\rightarrow$ distension of the capillary walls $\rightarrow$ leakage of fibrinogen from within the capillaries into the dermis and subcutaneous tissues of the calf $\rightarrow$ polymerization of fibrinogen into the dermis and subcutaneous tissues $\rightarrow$ pericapillary fibrin cuffs $\rightarrow$ prevent diffusion of O_2 and nutrients $\rightarrow$ ulceration.
- Macromolecules, e.g. fibrinogen and α_2 -macroglobulin that leak into the dermis as a result of venous hypertension "trap" growth factors, e.g. TGF- β , other stimulating, or homeostatic sub-

stances → the trapped molecules will be unavailable for the maintenance of tissue integrity and repair minor traumatic wounds → ulceration.

• Venous hypertension → ↓ pressure gradient between the arterial and venous systems → ↓ flow in the capillary bed between the systems → erythrocyte aggregation in capillaries & leukocyte plugging of the capillaries (**leukocyte-trapping hypothesis**). These trapped leukocytes become activated and they initiate an inflammatory response that leads to cellular and tissue dysfunction, resulting in the dermal changes often observed in patients with chronic venous insufficiency.

The cycle repeats itself:

Initial event → venous hypertension and VVs → lipodermatosclerosis → new thrombosis → stasis dermatitis → ulceration.

Other factors:

- MMPs: Increased expression and activity → breakdown of the extracellular matrix → promotes the formation of ulcers and impairs healing.
- Elevated TGF- β and VEGF → increased dermal fibrosis and proliferation of dermal capillaries, respectively.
- Capillary hyperpermeability and extravasation of red blood cells lead to deposition of ferric iron within affected skin, resulting in brown discoloration.
- Continued production of MMPs and cytokines (e.g. IL-1 and TNF- α) → impaired fibroblast function and increased degradation of growth factors necessary for wound healing.
- Oxidative stress → premature aging and dysfunction of wound fibroblasts contribute to the chronicity of venous ulcers.

Risk factors for venous ulcer

- Old age, obesity, with CVI of legs, history of significant leg injury, e.g. a broken leg, stab, phlebitis, deep venous thrombosis.
- Patients with VVs: Tend to be younger, female, history of phlebitis (post-phlebitic syndrome), +ve family history of VVs.
- A job that requires long hours of standing → slows the healing of venous ulcers.

Clinical presentations of CVI

- VVs.
- Reddish brown pigmentation and purpura.
- Stasis or venous dermatitis.
- Dependent edema.
- Atrophie blanche (AB) (38% of patients with CVI, but all patients with AB show symptoms of venous incompetence).

- In long-standing CVI, the surrounding skin becomes indurated and fibrotic involving the entire lower third of leg → an inverted champagne-bottle appearance.
- Lipodermatosclerosis (atrophy of skin & subcutaneous tissue & pigmentary changes) frequently precedes the development of venous ulcers.

Staging of CVI

- I Edema, ankle flare.
- II Lipodermatosclerosis, pigmentation, stasis dermatitis, AB.
- III All of the above + ulcers & scars.

- Venous ulcers (30% of cases): see table.

Assessment of CVI

Standardized evaluation of patients with chronic venous disease is based on the **CEAP** classification system:

C: Clinical signs.

E: Etiology.

A: Anatomical location of the affected veins (superficial, perforator or deep veins).

P: Pathophysiology (reflux, obstruction or both): Assessed by duplex ultrasonography. Venography is performed if an intervention is planned.

The 3 common types of leg ulcers ²

	Venous (Fig. 81)	Arterial (Fig. 82)	Neuropathic
Ulcer location	Medial malleolus between ankle & calf, trauma or infection may localize ulcers laterally or more proximally.	Distal, over bony prominences, trauma may localize ulcers proximally.	Pressure points on feet (e.g. junction of great toe & plantar surface, metatarsal head, heel).
Ulcer appearance	Shallow, irregular borders; base may be initially fibrinous but later develops granulation tissue.	Round or punched-out, well-demarcated border, fibrinous yellow base or true necrotic eschar; bone & tendon exposure may be seen.	Callus surrounding the wound & undermined edges are characteristic; blister, hemorrhage, necrosis & exposure of underlying structures are commonly seen.
Physical examination	Varicose veins, leg edema, atrophie blanche, dermatitis, lipodermatosclerosis, pigm. changes, purpura. Normal pulses & sensation.	Loss of hair, shiny, atrophic skin, dystrophic toenails, cold feet, femoral bruit, absent or ↓ pulses, prolonged capillary refilling time (>4-5 sec).	No sensation to monofilament; bone resorption, claw toes, flat foot, charcoal joints.
Frequent symptoms	Pain, odor & copious drainage from the wound, pruritus.	Claudication, resting ischemic pain.	Foot numbness, burning, paraesthesias.
ABI*	>0.9 (normal).	ABI <0.7 suggests arterial disease, calcification of vessels gives falsely high Doppler readings.	Normal, unless associated with arterial component.
Risk factors	Deep venous thrombosis, significant leg injury, obesity.	Diabetes, hypertension, cigarette smoking, hypercholesterolemia.	Diabetes, leprosy, frost bite.
Complications	Allergic contact dermatitis, cellulitis	Gangrene → amputation	Underlying osteomyelitis.
Treatment pearl	Compression therapy, leg elevation.	Pentoxifylline, vascular surgery assessment if ABI <0.5.	Vigorous surgical debridement, pressure avoidance.

* Ankle/brachial blood pressure ratio index (ABI).

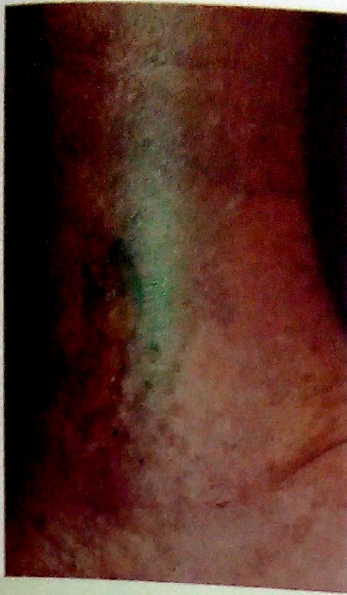


Fig. 81. Venous ulcer



Fig. 82. Arterial ulcer

Treatment of leg ulcers ²

I) Moisture and occlusion

In the past, the mainstay of wound management was to dry the wound bed, but now: Moist environment is critical for wound healing (attention to the delicate balance between overhydration and excessive dryness).

Moist retentive wound dressings:

- Stimulate collagen synthesis.
- Promote angiogenesis by creating a hypoxic environment.
- Encourage re-epithelialization.
- Decrease pain.
- Barrier against external contamination + lowering wound pH → decrease wound infection rates.

II) Debridement

Removal of necrotic, non-viable or infected tissue from the wound bed promotes healing, but this is better avoided in arterial occlusive diseases because it can cause further ischemia.

- **Sharp debridement** with surgical instruments
- **Wet-to-dry** (mechanical) debridement: Placing gauze moistened with saline over the wound, allowing the gauze to dry, and then removing the dry gauze along with adherent non-viable tissue.
- **Autolytic debridement**: Body uses its own proteolytic enzymes and phagocytic cells to clear necrotic debris. The process is enhanced by moist retentive wound dressings and may require weeks to accomplish.
- **Enzymatic debridement**: Topical application of proteolytic enzyme preparations such as papain-urea or collagenase to digest necrotic tissue.
- **Maggot debridement**: Maggots (benign myiasis) → proteinases to decompose necrotic tissue.

III) Wound dressings

- **Gauzes:** For wet wounds with heavy exudate.
- **Films:** For wounds with minimal exudate.
- **Hydrogels:** For dry wounds.
- **Collagens:** For clean, non-infected, recalcitrant chronic wounds.

IV) Management of wound infection

- Clinically infected wounds should be cultured & treated initially with broad-spectrum systemic antibiotics. The antibiotic regimen is then adjusted based on the results of sensitivity testing.
- Colonization is presence of replicating bacteria & adherent microorganisms without evidence of tissue damage, but it delays healing.
- In properly treated, non-healing wounds that demonstrate critical colonization, topical antibiotics should be considered.

V) Adjuncts to wound care

Compression:

- It is the mainstay in the treatment of venous insufficiency.
- Compression therapy in undiagnosed arterial insufficiency → ulcer worsening, gangrene & even limb amputation.
- Types of compression therapy: Elastic wraps, self-adherent wraps, Unna boot, ...

Manual lymph drainage:

- Edema is a significant cause of delayed healing of venous ulcers.
- Manual lymph drainage is a massage technique including series of exercises to increase lymphatic flow through functioning collateral pathways.

Topical negative pressure therapy:

- Using a vacuum assisted closure (VAC) system to create mechanical forces that stimulate biological response to enhance healing.
- It is contraindicated in ischemic wounds (necrosis of the wound edges) & ulcerated malignancies (tumor growth).

Skin substitutes:

- Autologous skin grafting
- Living skin substitutes are tissue-engineered products that contain a cellular component of autologous or allogeneic origin plus a biodegradable scaffold.
- Biological dressings: Consist of just an extracellular matrix (i.e. they have no cellular component), such as collagen, fibronectin and proteoglycans.
- Bio-inspired artificial hydrogel matrix that utilizes natural enzymatic reactions to become bioactive.

Topical and oral medications

- Daily, short-contact application of topical tretinoin → stimulates granulation tissue formation & induce neovascularization in ischemic wound beds.
- Hyperbaric oxygen has a specific benefit to patients with diabetic foot ulcers.

- Genetically engineered exogenous growth factors: Becaplermin gel (Regranex®): Recombinant platelet-derived growth factor → stimulation of granulation tissue production and release of other growth factors important to wound repair.
- Pentoxifylline.

V) Specific treatment

For **varicose veins**

1. Surgical options

Surgical options in treating varicose veins	Complications of varicose vein surgery
• Total saphenous vein stripping. • Segmental saphenous vein stripping. • Saphenous vein ligation, high, low or both. • Saphenous vein ligation & sclerotherapy. • Saphenous vein stripping & avulsion of varices. • Stab/avulsion of varices without saphenous vein stripping.	• Excessive scarring. • Wound infection • Cutaneous pigmentation. • Superficial thrombophlebitis. • Deep venous thrombosis. • Pulmonary embolization. • Recurrence of varicosities. • Telangiectatic matting. • Saphenous neuropathy.

2. Sclerotherapy treatment of varicose veins

Definition: It is the injection of aqueous solutions into abnormally dilated or cosmetically unacceptable veins to produce stenosis and fibrosis.

Sclerosant: It is the material used in sclerotherapy. Usually:

- Sodium morrhuate.
- Sodium tetradecyl sulphate (sotradecol band).

Contraindications

- Pregnancy.
- Bed-ridden patient.
- Diabetic patient.
- DVT.
- Obesity.
- Arterial obstruction.
- Hypersensitivity reaction.

Principles of varicose vein sclerotherapy

- Proximal to distal.
- Largest veins before smaller veins.
- Vein must be emptied of blood by various maneuvers.
- Direct finger pressure in a spreading & compressing motion after injection.
- Entire varicosity is treated at one time.
- Reflux points determined initially & treated specifically.
- Immediate & adequate compression.
- Adequate ambulation immediately after treatment.

For arterial insufficiency

Restoration of peripheral arterial blood flow, either by surgical reconstruction (e.g. femoral popliteal bypass) or by less invasive endovascular interventions (e.g. femoral angioplasty).

Pressure ulcers

Synonyms: Bed sores, pressure sores, decubitus ulcers and ischemic ulcers.

Definition: Pressure ulcers are localized areas of tissue necrosis that tend to develop when soft tissue is compressed between a bony prominence and an external surface for a prolonged period of time.

Sites: Areas of skin overlying bony prominences. These include the sacrum, ischial tuberosities, greater trochanters, heels and lateral malleoli. 95% of all pressure ulcers develop on the lower portion of the body.

Classification

- **Stage I:** Non-blanchable erythema of intact skin, a herald sign of skin ulceration.
- **Stage II:** Partial thickness skin loss that may involve the epidermis or dermis, which presents clinically as an abrasion, blister or shallow crater.
- **Stage III:** Full-thickness skin loss that involves the subcutaneous tissue and may extend down to but not through, the underlying fascia.
- **Stage IV:** Full-thickness skin loss but with involvement of muscle, bone, or supporting structures such as tendon or joint capsule.

Epidemiology

- Acute care hospital settings: 3-14%.
- Long-term care setting: 15% to 25%. Among patients with spinal injuries (20-30%).
- Home care settings: 7% and 12%.

Histopathology

- Epidermal necrosis with eccrine duct and gland necrosis. Neutrophilic & mononuclear infiltrate around necrotic eccrine glands.
- Deep ulcers show wedge-shaped infarcts of the subcutaneous tissue, obstruction of the capillaries with microthrombi and endothelial cell swelling followed by endothelial cell necrosis and secondary inflammation.

Pathophysiology

- External compression of dermis and hypodermis → ischemic tissue damage and necrosis.
- The four major etiologic factors involved in the development of pressure ulcers are pressure, shearing forces, friction and moisture.

Risk factors

- Prolonged immobilization: The incidence of pressure ulcers is inversely related to the number of nocturnal movements.
- Sensory deficit: Spinal cord injuries sensory loss.
- Circulatory disturbances.
- Poor nutrition.

Complications

- Pressure ulcers can be complicated by several conditions, which can at times be life threatening.

- These include: Infection, sepsis, osteomyelitis, fistulas and carcinoma.

Management

- **Prophylaxis in at-risk patients:** Reposition patient every 2 hrs (more often if possible), massage areas prone to pressure ulcers while changing position of patient, inspect for areas of skin breakdown over pressure points.
 - Use interface air mattress to reduce compression.
 - Minimize friction and shear forces by using proper positioning, transferring and turning techniques.
 - Clean with mild cleansing agents, keeping skin free of urine and feces.
 - Minimize skin exposure to excessive moisture from incontinence, perspiration or wound drainage.
 - Maintain head of the bed at a relatively low angle of elevation (<30 degrees).
 - Evaluate and correct nutritional status, consider supplements of vitamin C and zinc.
 - Mobilize patients as soon as possible.
- **Stages I and II ulcers:** Topical antibiotics (not neomycin) under moist sterile gauze may be sufficient for early erosions. Normal saline wet-to-dry dressings may be needed for debridement. If ulcer does not heal by 30% within 2 weeks, consider hydrogels or hydrocolloid dressings.
- **Stages III and IV ulcers:** Surgical management includes: debridement of necrotic tissue, bony prominence removal, flaps and skin grafts.
- **Infectious complications continuous osteomyelitis:** Prolonged course of antimicrobial agent depending on sensitivities, with or without surgical debridement of necrotic bone.
- **Sepsis:** Marked by elevated temperature, chills, hypotension & tachycardia, &/or tachypnea. Massive antibiotic treatment according to antibiogram.

alltebfamily.com